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DIABETIC Medicine

REVIEW ARTICLE

Centenary of Insulin

100 years of physiology, discrimination and wonder

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Abstract

There has been 100 years of research detailing the role of insulin in glucose, protein and free fatty acid metabolism. We explore the learnings though evolution and changes in management with an understanding of how it has impacted the care of people with diabetes. The discrimination endured is described and recent advances to empower and counter this are highlighted.

KEYWORDS

evolution, insulin, type 1 diabetes

1 | INTRODUCTION

With the discovery of insulin, there has been 100 years of research detailing the pivotal role the hormone plays, not only in glucose metabolism but also in protein, free fatty acid and lipid metabolism.[1–3] These contribute to the maintenance of functioning organisms as well as growth and development. Insulin-like molecules have been discovered in very simple animals and have been highly conserved throughout evolution.[3] This conservation or lack of divergence throughout evolution highlights the importance of the hormone in the regulation of life.[3] This has had the advantage that animal insulins work in humans and this is unlike growth hormone where primates have diverged.

In simpler animals, insulin had both the growth-promoting and metabolic role, and in higher animals with splitting off of IGF-1, IGF-2 and growth hormone, there has been a subtle difference between growth-promoting activities of these more recent hormones and that of insulin whose primary role is minute by minute energy regulation and regulation of all aspects of metabolism.[4] Although insulin is well known for its control of glucose homeostasis, it also plays a critical role in many other metabolic processes. Most prominent of these is probably protein metabolism which has received less prominence but is equally, if not as important as glucose regulation.[2] Furthermore, insulin has a major controlling effect on free fatty acids and lipid metabolism. There has also been an expansion in literature and interest in its importance in the brain.[5,6] Thus, this hormone that is known throughout the world for the last 100 years as the glucose-regulating hormone also plays vital roles in the many other systems that are gaining more prominence.

2 | INSULIN PHYSIOLOGY—GLUCOSE

Blood glucose levels are tightly controlled by insulin. Insulin achieves this by supressing endogenous glucose production by the liver through a direct receptor-mediated action of inhibiting glycogenolysis and by suppressing gluconeogenesis.[7] The indirect effects of insulin include the reduction of glucagon secretion from the pancreas, inhibition of lipolysis in adipose tissue and reducing amino acid released from muscles reducing substrates for gluconeogenic pathways.[8] There is also mounting evidence of direct effects via the brain in neurally driven pathways predominantly originating from the hypothalamus.[9] In

concert with the suppression of hepatic glucose output, insulin stimulates peripheral glucose uptake in peripheral tissues—predominantly adipose and muscle.[3] These two synergist actions reduce blood glucose levels rapidly. It is hardly surprising that insulin production is situated close to the liver and indeed the hepatic portal vein in mammals directly delivers insulin at 4–5 higher concentration than the systemic circulation to its major target organ the liver.[3] In mammals, unlike vertebrates and birds, a defined and separate portal system to enable direct rapid vascular communication has evolved. This portal link also allows an additional subtlety of first-pass insulin extraction, which can amount up to 50% of the total insulin extraction.[10] This extraction is largely receptor mediated and thus the affinity of mammalian insulin to the insulin receptor plays a major role in the balance of how much insulin reaches the systemic circulation beyond the liver and accordingly an additional control of metabolism within the body.[3,10]

This explains why mammalian insulin appears to have taken a slight retrograde step to have less affinity for its receptor than some vertebrate and avian insulins (see evolution).[3] Insulin also has a differential effect on metabolism depending on its concentration in the bloodstream. With increasing insulin levels, hepatic glucose output is suppressed, and when this is almost complete, there is increasing peripheral glucose uptake with increasing insulin concentration which has a different dose–response curve allowing additional uptake even at relatively high concentrations of both glucose and insulin. The uptake in periphery is also in part regulated by glucose concentration, that is the higher the glucose level, the greater the peripheral uptake, which is enhanced by insulin in insulin-sensitive tissues.[3,5] The subtleties and nuances on glucose metabolism is continually being investigated and updated.

3 | INSULIN PHYSIOLOGY—NOT JUST GLUCOSE

While glucose homeostasis is all about energy conservation and utilisation for the integrity and activity of an organism, protein metabolism takes a possibly greater remit in that all of the structural elements and enzyme pathways are protein dependent and insulin plays a major role controlling protein metabolism within organs and individual cells including a pivotal role on growth.[2] Insulin is credited for having a major action on proteostasis, which is the regulation of the proteome (all of the protein activity within the cells and organism). At the whole-body level, insulin has a major action to reduce proteolysis and thus has an anabolic action by reduction of predominantly protein breakdown.[2] In certain tissues, however, insulin has a protein synthetic action and can even have a differential action across different organ systems, for example the liver during different physiological circumstances.[2]

Having a hormone that can both regulate energy metabolism and growth and development and metabolic function illustrates its importance to life and the reason it is so highly conserved throughout evolution.[3]

In addition to the effect on protein metabolism, insulin has a direct effect to suppress lipolysis and liberation of free fatty acids and thus regulates the other major fuel energy supply for metabolism of the body. Subtle and interesting effects on lipid metabolism, for example its direct effect to reduce B100 VLDL production, illustrate its wide action across the metabolic field.[5] The preponderance of insulin receptors in the brain has always led to speculation of a major role and recent physiological studies are beginning to elucidate the importance within the central nervous system.[6]

4 | EVOLUTION OF THE INSULIN MOLECULE

The evolution of the insulin molecule is fascinating. The identification of the pancreas as the origin of diabetes mellitus by von Mehring and Minkowski in 1889 led to the successful extraction and introduction of the active principle, insulin, in 1921 by Banting, Best, Collip and Macleod. Some researchers thought insulin was an exclusive hormone present in mammals and birds alone. Insulin is in fact present in invertebrates and vertebrates. It is produced from the pancreas, except in primitive jawless vertebrates, for example hagfishes (Myxiniformes) and protochordates where it originates from the bile duct-associated islet parenchyma.[11]

In 1923, Collip reported insulin action in the bivalve mollusc, *Mya arenaria*. Using advances in technology, there was a quick succession of insulin isolation and sequencing. By 1975, insulin molecules had been classified in all vertebrates. The isolation of invertebrates was slower, taking a further 10 years before Nagasawa et al. purified an insulin-like molecule from the silkworm *Bombyx mori*.[11]

More recently, recombinant DNA has been used to clone insulin-like peptide genes from a variety of vertebrates and invertebrates.[12]

Progressive technology has enabled us to trace the evolution of amino acid configuration. It is evident that strong evolutionary pressure has conserved the amino acids thought to be important in the biologically active conformation.[13] Key surface residues that have been preserved through evolution include the following: A chain amino acids—Gly A1, Gln A5, Tyr A19 and Asp 21—and

B chain amino acids—ValB12, Tyr B16, Gly B23, Phe B24, Phe B25 and Tyr B26.[3]

Hagfish (Myxiniformes) insulin is very interesting—it has reduced affinity for mammalian insulin receptors.[14] It is thought that the diminished biological activity results from unfavourable substitutions, namely A10 (Ile to Arg), B4 (Glu to Gly), B13 (Glu to Asn) and B21 (Glu to Val).[3] Primitive amphibian Amphiuma insulin is remarkably similar to human insulin. It contains a histidine A8 residue that is surmised to be responsible for its fivefold higher affinity than pig insulin for binding to the human insulin receptor.[15]

Among mammals (except hystricomorphs), functional species differences are minimal such that bovine and porcine insulin can both provide effective insulin replacement treatment in people with diabetes. However, mammalian insulin does not have a histidine A8 residue. In contrast, most bird insulins do retain the A8 histidine residue and notably have higher binding affinities for mammalian insulin receptors than their own native insulins.

5 | MANAGEMENT OF TYPE 1 DIABETES OVER TIME

Before the discovery of insulin, the only treatment for people with type 1 diabetes was extreme diets, of which the notorious Jocelyn Starvation Diet, although potentially prolonging life, ultimately led to starvation.[16] Other milk or beef tea diets were promoted in the United Kingdom with disappointing results.[17] The miraculous transformation following the discovery of insulin for people with type 1 diabetes is still one of the wonders of medical science. In 1978, the first successful production of human insulin was produced by recombinant DNA technology in *Escherichia coli*. This was achieved by a team of specialists led by Robert Crea and David Goeddell. Insulin became the first genetically manufactured drug to be approved by the FDA. In 1996, the FDA approved the first insulin analogue, insulin lispro.

In the current era, it is always important to reflect on how insulin treatments have changed in 100 years for people and also the whole nature of care and healthcare delivery to people with type 1 diabetes. In the preface to the first edition of R. D. Lawrence's seminal work 'The Diabetic Life' (1925),[18] he states, 'Five years ago *Diabetic Death* would have been a more suitable title for such a book as this than *The Diabetic Life*'. He went on to state, 'I make no apology to doctors for writing a combined book for them and their patients for the latter invariably come to know a great deal about their illness'.[18] This highlights the sea change in treatment possibilities over just a short number of years and the genius of Lawrence to foresee the vital role of participant empowerment in managing their condition.

Following the introduction of insulin, there have been many advances in self monitoring techniques to support insulin administration. In the early years, people were injected with insulin syringes, insulin was supplied in rubber top bottles and sterilised the insulin needles with methylated spirits. The year 1972 saw the introduction of the first community-based and then hospital-based diabetes specialist nurses to support people with diabetes.

Quantifying glucose in urine was the main form of participant monitoring. In 1945, the development of Clintest was launched which featured a modified copper reagent tablet. Glucose was oxidised, and the amount of glycosuria was proportional to the colour of the heated solution.[19] In 1978, the first blood glucose metre was launched. The adjustments of insulin dosage and type were found to be much easier and more predictable than with urine glucose analysis.[20] The Gluco Chek was designed and revolutionised self monitoring with the possibility to reduce the incidence of long-term diabetes complications. Blood glucose monitoring is now part of standard care.[21]

The introduction of the first Insulin pen occurred in 1985, leading to improvement in accuracy, participant satisfaction and adherence and quality of life. Insulin pump therapy was launched in the 1990's. In 1999 saw the first continuous glucose metre approved by the US Food and Drugs Administration (FDA) although people were blinded to the data which required the data to be downloaded by healthcare professionals.[19]

The future looks exciting, with advancement in self management technology such as flash glucose monitoring systems and real-time continuous glucose monitoring. The widespread clinical use of continuous glucose sensors and insulin pumps has enabled a steady progress for the development of artificial pancreas. Insulin delivery systems in combination with glucagon are further in development and people continue to drive advances with Do It Yourself (DIY) closed loop systems (looping) technology.

6 | THE PARTICIPANT PERSPECTIVE

To further emphasise the impact of the changing decades on management, not only with insulin but across the range of clinical and social care, we surveyed a range of people who have diabetes and are recipients of the Nabarro (50 years), R.D. Lawrence (60 years) and MacLeod (70 years) medals for living with diabetes. They were asked to provide words or phrases to sum up all aspects of living with diabetes. Their views and recollections of what it was like when they were first diagnosed

have been put into a word clouds (Figure 1). In contrast, we have asked young adults and children with diabetes from the current generation to do similarly (Figure 2). The differences between the generations shown in these word clouds serve beautifully and graphically to illustrate the advances made in clinical care.

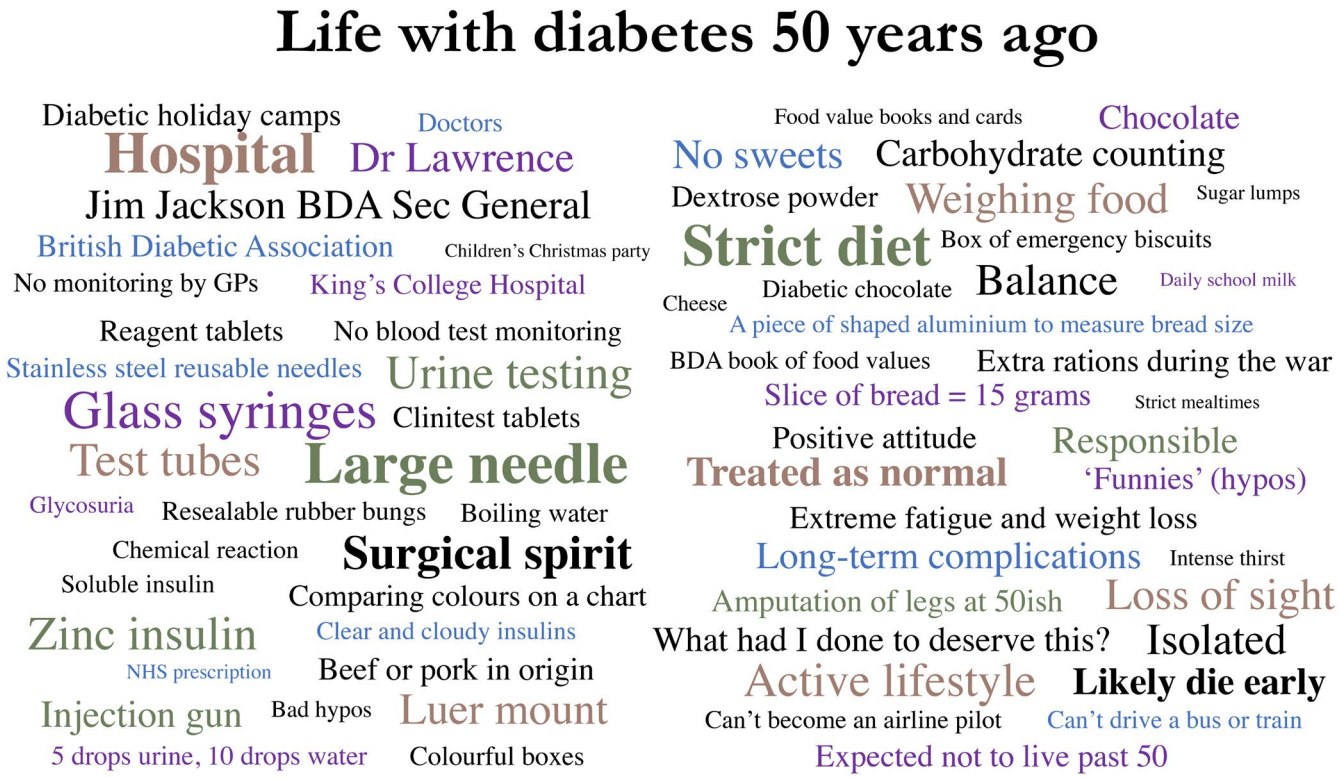

FIGURE 1 Views and opinions of people diagnosed with type 1 diabetes 50 years ago

FIGURE 2 The current generation, opinions from children and adolescents living with diabetes today

Prior to the discovery of insulin type 1 diabetes was a lethal condition with little hope of survival. With the initial introduction of rudimentary and primitive insulin regimes, the object of care was simple survival. This was characterised by rigid dietary rules and severe glucose instability leading to dramatic symptomatic hypo and hyperglycaemia. With low self-esteem and the frequent development of chronic complications leading to blindness, amputations and kidney failure, it is hardly surprising that societies' view was that type 1 diabetes was a disabling and debilitating disease.[22] With the lack of understanding and poor monitoring, people experienced significant discrimination at school, work and during leisure activities.[22] With the advent of accurate monitoring and vastly improved clinical care, these attitudes have been challenged.[23]

The Equality Act 2010 protects people with type 1 diabetes from discrimination at work, and requires an employer to make reasonable adjustments for employees and job applicants who are disadvantaged as a result of their disability, like taking a short break to treat a hypo or check their blood glucose level.[24] The International Diabetes Federation launched an International Charter of Rights and Responsibilities for People with Diabetes in 2011.[25] The overall goal of this charter was to reduce the barriers which deny realisation of full potential as members of society but had to be balanced by public safety.[25] The aim of this charter was to boost health and quality of life, enable as normal a life as possible and to reduce and eliminate barriers that deny realisation of full potential as members of society as a whole. It was stipulated that people should be treated fairly in employment and career progression while acknowledging that there were certain occupations where identifiable risks may limit the employment.[25] The risk of incapacitation through hypoglycaemia is the most widely quoted reason for a blanket ban on safety-critical occupations being performed by people with diabetes managed with insulin.[23] With the advent of modern care, much has been achieved to overturn and change perception. One area that exemplifies this progress is in the ability of people treated with insulin to be allowed to pilot aircraft both non-commercial and commercial.[26] The recent published experience of the United Kingdom, Ireland and Austria of safety using a traffic light protocol for in-flight glucose monitoring by pilots has been heralded as a major advance,[26] demonstrating that safety-critical occupations can be performed by insulin-treated people.

Despite many efforts, there are still some positions that do not allow people to work who have diabetes. The emergency services have lifted bans for people with type 1 diabetes and type 2 diabetes using insulin leaving the decision to the local services. For example, some NHS Ambulance Trusts have rules about people with diabetes applying for jobs as ambulance crew. In addition, the UK armed forces are exempt from the Equality Act and have a blanket ban on employing people with diabetes.[27]

Great progress has been made, and with such successful initiatives, discrimination is likely to become less in the future years.

7 | CONCLUSION

In the 100 years since the discovery of insulin, some of the greatest advances in medicine have occurred studying diabetes. Insulin plays a fundamental role in metabolism and growth and has been highly conserved in evolution illustrating its importance. Strong evolutionary pressure has led to subtle changes which can be explained by understanding physiology. Treatment with insulin has evolved leading to new generations of people with diabetes experiencing very different care and relying on different tools to achieve good control. These improvements have allowed discrimination to be challenged.

CONFLICT OF INTERESTS

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