Supporting veterinary medicine in diabetes research a win-win approach for animal welfare and human health

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Diabetes is one of our most common diseases, and it severely affects patient quality of life. Uppsala University together with SLU (Swedish University of Agricultural Sciences) are now mobilizing forces within diabetes research by establishing a multidisciplinary center focused on preventing and treating the disease – the Uppsala Diabetes Centre (UDC).

Most people suffer from type 2 diabetes. However, among Swedish children, type 1 diabetes is the most common chronic disease, one that currently lacks a cure. For still unknown reasons, the occurrence of type 1 diabetes has doubled in the last 30 years and continues to increase by about 5 per cent per year. The demand for more effective treatments is considerable but so far research has been unable to identify satisfactory treatment methods, even with major efforts. Myself I got Diabetes Type 1 for over 36 years ago and indeed knows how it is to live with this disease! This motivates me every day to work towards better diagnostic, treatment and prevention for it!

The new center – the Uppsala Diabetes Centre (UDC) – is bringing together expertise in human- and veterinary medicine, pharmacology, natural sciences, engineering, social sciences and the humanities to leverage different perspectives in solving the challenges of preventing and treating diabetes.

Below follows a high-level description of the different diabetes types found in animals. At each type an explanation of the comparative aspect with human diabetes is clarified. Of the non-clinical human studies the vast majority of all diabetes research today is centered on *in vitro* studies and rodent models. The somewhat low success rate in applying findings in these experiments into human diabetes medicine clearly calls for additional models to be investigated. Within veterinary medicine, diabetes mellitus has been recognized for over hundred years. Recently strong scientific support suggests that using spontaneous models of diabetes in dogs, cats and horses may mimic diabetes in humans sometimes even superior to more conventional experimental models. Funding this research will enable a better understanding of the disease in animals, increasing the possibility to enhance animal welfare and health. Simultaneously the research findings may closer mimic the actual biology in man and hence fasten the improvement of quality of life and prognosis for humans with diabetes type 1 and 2. Finally, the genetic predisposition in animals will ease the genomic endeavors to find genetic predisposition for diabetes and hopefully better prevent diseases also in man.

The possibilities of animal diabetes models and to increase the focus on diabetic patients in the veterinary clinic are currently heavily underutilized.

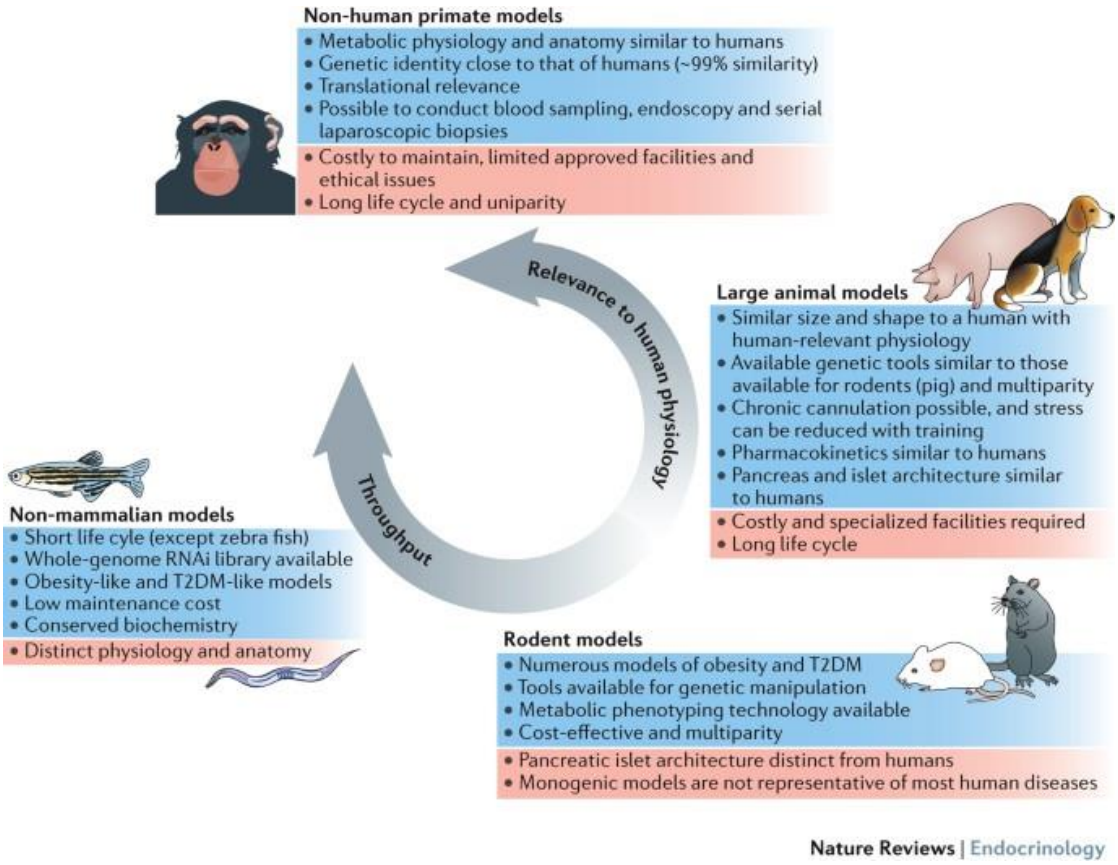

Figure showing the different animal models used in human diabetes research. The vast majority is performed in rodents and non-mammalians. Note that the two limitations mentioned in large animal models do not imply for sport and companion animals with spontaneous disease. Long life cycle is circumvented as the animals that show up at the clinic already have the disease. Costly and specialized facilities are already there as functional animal hospitals with state-of-the-art diagnostic and treatment modalities. (from: Kleinert, M. et al., Nature Reviews Endocrinology volume 14, pages 140–162 (2018))

Canine (dog) model

In dogs several types of diabetes exists. The most common type is the Diabetes Mellitus Type 1. Other types commonly seen is Gestational Diabetes and Iatrogenic Diabetes due to treatments with drugs that are causing Insulin resistance, like progesterone and steroids (cortisone). Finally, diseases like Cushing Disease can cause diabetes in dogs. Diabetes type 2 is rarely seen. With increasing knowledge of the disease in dogs and a higher interest in treating dogs in general, insulin treatment is now very common. Trained personnel teach owners, blood glucose monitoring is done at home and interpreted and discussed at regular re-visits at the specialized veterinary internist/endocrinologist. Just as in human diabetes treatment. Late onset complications in retina and kidneys do exist and are monitored by ophthalmologists and internist/nephrologists. As in man, good glucose control is prognostic for survival and quality of life. There are specific canine insulins now registered. Gestational diabetes is common in dogs and will be controlled with birth or ending of sex-hormone signaling. If the diabetes is present for a longer time, insulin treatment will be required. Clear breed-predisposition has been found for the development of gestational diabetes, showing that a genetic risk factor likely is present.

Figure showing Golden Retriever puppies entering the University Animal Hospital at SLU for donation of samples to the Dog Genome Biobank. Imagine if the dog once again creates significant scientific breakthrough in the treatment of Diabetes Type 1 in humans as it did back in 1923? This very dog may end up leading to research discoveries that will safe this girl's life years from now thanks to the rapid exploration of the canine genome, work of skilled veterinarians and human doctors and comparison with similar diseases in man!

Comparative aspects

As in man, the diabetes in dogs is spontaneous. The presence of autoantibodies is not clearly verified. However, strong support of the autoimmune T-cell response seen in human diabetes type 1 has been presented. As the dog responds identical to insulin treatment, have spontaneous disease and with a body size that enables testing full-sized human devices (such as insulin pumps, implanted gluco-meters etc) it serves as a very good clinical model for human diabetes type 1. The current standing is that canine diabetes type 1 mostly resembles the human LADA (Latent Autoimmune Diabetes in Adults) typically occurring in young adults.

The gestational diabetes seen in dogs is very interesting as we see such a clear breed predisposition. Hence, the possibility to find genetic predisposition is much easier than in humans. This, as dog breeds will have a much higher similarity between individuals and thus faster to find genetic "hot-spots" to further analyze. Then, it is easier to compare the human genetic counterpart, as the dog-genome now is sequenced at a very high resolution that makes these comparisons easier. Studying Gestational Diabetes in dogs is much better done in Sweden compared to e.g. the USA, as early prophylactic neutering is not performed as commonly in here. Hence, we have many more cases to study and sample.

Finally, one should not forget that the first successful treatment of a child with Diabetes Type 1 was done with insulin from a dog. This was the final proof-of-concept for Insulin and led to the Nobel Prize in 1923 for Frederick G. Banting and John Macleod. There is no reason for why new groundbreaking findings for human Diabetes Type 1 would not come from canine studies!

Feline (cat) model

The Feline Diabetes is a typical Type 2. Predisposing factors are overweight and chronic pancreatitis. As the cats have been more supported with commercial feed, being more indoors (inactivity) and as in dogs, gaining a higher interest in treating/supporting a longer life, the occurrence of Diabetes has increased. In cats, introducing Lantus Insulin early in disease onset and reducing BMI, often put the cat into remission and hence Insulin is no longer needed to control blood glucose. If symptoms are present too long, Insulin resistance will be permanent and Insulin treatment mandatory for survival. As in dogs, cats are common patients at the clinics with controls of long-term glucose (HbA1c/Fructosamine) and potential complications in different organs.

Diabetes in cats is very common. Typically, they present with type 2 diabetes. The feline model is suggested as an excellent model to study the crosstalk between chronic inflammation/obesity/pancreatitis. The cats show identical response to long-acting insulin (e.g. Lantus) as humans and can sometimes become independent of insulin treatment after reduced weight and diet change, again similar to man. Some pure breeds have a higher tendency to develop diabetes, indicating a predisposed genetic cause. If this is identified, comparison with the highly homologous human genome sequence can be made and new treatments and likely prevention can emanate from these findings.

Comparative aspects

Cats have a typical Type 2 Diabetes and respond as humans on reduced body weight and early Insulin treatment. As there is a clear breed predisposition also in cats, the possibility of doing genetic studies in pure breed cats will possibly find genetic risk factors for Diabetes Type 2 that will be easily compared with the human genome. As in dogs, the feline genome is sequenced with a high resolution and with a very high homology towards the humans. In Sweden, we have a very good identification of pure breed cats and a dedicated group of owners and breeders, making a large-scale study of feline diabetes possible!

Equine (horse) model

In horses, it has long been known that overweight/over fed horses has a much higher risk to develop laminitis (*fång in Swedish*). Especially in ponies and some thoroughbred. The disease is now identified as equine metabolic syndrome (EMS). The term EMS was first introduced in 2002 after similarities were seen between horses at risk of laminitis and the human 'metabolic syndrome' that describes a collection of risk factors for Type 2 Diabetes and cardiovascular disease. Initially, EMS was defined as the combination of obesity or regional fat depots,

current or previous laminitis and insulin resistance. As research continues, the definition of EMS has evolved and today can perhaps be best described as being a collection of risk factors associated with an increased risk of laminitis including 'insulin dysregulation' (as opposed to insulin resistance). Although affected horses are typically overweight/obese, EMS also occurs in lean or underweight horses.

Equine metabolic syndrome includes insulin resistance and is often seen in overweight horses. Some do even develop diabetes (type 2). As many similarities with human metabolic syndrome exists, the horse has been suggested as an excellent model for human diabetes research.

Comparative aspects

As the same risk factors are present in horses as in man for Diabetes Type 2 and the horse is a very easy animal to get specimens from and get a large sample size, it is a very attractive model to further investigate. As laminitis is a huge animal welfare issue the comparative diabetes research in horses could gain results that both decrease animal suffering and increase human health simultaneously. As in dogs and cats, the equine genome is being increasingly sequenced in high resolution. Since EMS is seen in many thoroughbred, the potential to easier find genetic hot spots for development of Insulin Resistance can rapidly be transferred into homologous areas in the human genome and faster investigated than if the same research only was carried out in man.

Porcine (pig) model

Differently to dogs, cats and horses the pig model does not offer a spontaneous model to human diabetes. However, it still stands out as one of the most important models for Beta-cell transplantation to treat poorly controlled Type 1 Diabetes in man. Furthermore, implantation of remotely readable gluco-meters are finally tested in pigs, as their body size and similar glucose control as in humans, make the real human devices possible to test and be refined in the pig. Finally, kidney transplantation is best studied and refined in pigs. Kidney failure is regrettably a common sequel of Diabetes in man. Thus, many of the patients needing kidney transplants are also diabetic.

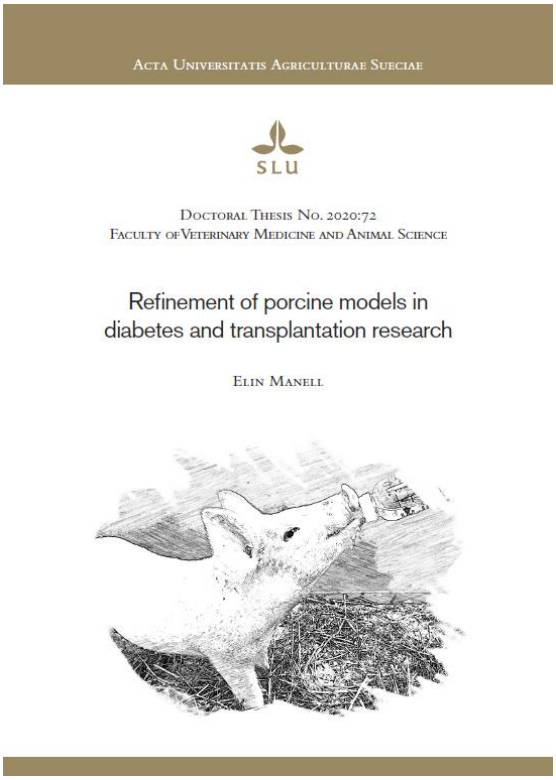

Figure showing the front page of a recent thesis from the VH-faculty at SLU from Dr Manell that illustrates the important studies within diabetes and renal transplantation research with the pig as an excellent model performed at SLU.

Comparative aspects

The pig model is a true comparative (experimental) model. As the scarcity of Beta-cell donors still is high in people and the survival of the implants still needs to be improved, the pig model is extremely important! In the pig, all the equipment used in the human transplantations are identical, thus enabling proper training of transplantation surgeons to minimize failures in human patients. In pigs, one can also try new protocols that will enable fewer cells to be transplanted, with still kept effect. Thus enabling more patients to be treated with the same amount of Beta-cells. Finally, new treatment regimens and pre-treatment of Beta-cells can be tested to increase the survival and function of the transplants in people. At SLU we have a state-of-the-art facility for pigs, as well as expertise in porcine medicine, anesthesia and pig welfare. With the use of animals for scientific purposes comes the responsibility to treat the animals in the best possible way and to assure that accurate and relevant data is collected. In 1959, Russel and Burch published 'The Principles of Humane Experimental Techniques' in which they introduced the terms replace, reduce and refine (3Rs). While it is desirable to replace animal models in research, they are still necessary and therefore it is essential to use the best methods possible to reduce the numbers of animals needed, and to refine procedures to minimize pain, suffering and distress. The 3Rs have become internationally recognized and are considered in, for example, the EU legislation on the protection of animals used for scientific purposes (EU, 2010) and US guidelines for the care and use of laboratory animals (NRC, 2011). The overall aim of the pig experimental studies at SLU is to work with refinement of porcine models in diabetes and renal transplantation research.