Healthy ageing and longevity in dogs - a lifelong approach

Perspectives from Internal Medicine, Orthopaedics, Oncology, Nutrition and Practice Management

Eukanuba Veterinary Symposium

Pre-Congress Symposium at the VetMadrid 2015, the XXXII AMVAC Annual Congress

Madrid, Spain

March 5th, 2015

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XXXII Congreso Anual de AMVAC Vet madrid 2015

Introduction

Welcome to the Eukanuba Veterinary Symposium, a Pre-Congress Symposium of the VetMadrid 2015, the XXXII AMVAC Annual Congress. We would kindly like to thank the organisers for hosting our Symposium and for their support in its organisation.

Attempts to develop theories of ageing, mortality and lifespan have deep historical roots.[1] In 1825 Benjamin Gompertz discovered the law of mortality: the force of mortality increases with geometrical progression with the age of adult humans. But do our ageing canine companions parallel what is seen with humans? Exploring the biology of longevity and successful ageing in dogs is challenging, but the rewards can be great. In a recent issue of *The Veterinary Journal*, reporting on results from a canine longevity study,[2] the authors begin their paper: '*Improved understanding of longevity represents a significant welfare opportunity for the domestic dog*'. Therefore, there is a need to further understand ageing and the positive role that everyday veterinary medicine can play in canine longevity through a lifelong approach.

We are very pleased to bring together our expert guest authors to help explore ageing and longevity through a number of different disciplines. Each will share the latest science and thinking from their area of expertise that can be adopted and implemented into everyday clinical practice to further help promote healthy ageing and longevity.

While we still do not have all the answers on canine ageing and longevity, we can however look to consider adapting our future research approach through adopting two key concepts:[3] *Life course perspective* is the concept that early life events can significantly influence adult health outcomes, including longevity.[4] The second concept is *whole organism thinking*, which can teach us to see all interventions made during life as both good *and* bad and not just as good *or* bad.[5]

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March 2015

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Dr Penny Watson is a Senior Lecturer in Small Animal Medicine at the Queen's Veterinary School Hospital, Cambridge, UK. She holds the Royal College of Veterinary Surgeons (RCVS) Certificate in Veterinary Radiology and Diploma in Small Animal Medicine, is a Diplomate of the European College of Veterinary Internal Medicine and a former head examiner of their Internal Medicine Diploma exam (DipECVIM). Penny Watson's research focuses on liver and pancreas disease in dogs and cats, particularly chronic disease and fibrosis. Her research has defined the prevalence of pancreatic lesions at post-mortem and breed-related differences in pancreatic pathology which suggest differences in aetiology between breeds. Dr Watson also runs a busy internal medicine teaching and referral clinic at the veterinary school and is Honorary Secretary of the British Small Animal Veterinary Association.

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Stuart Carmichael graduated from University of Glasgow in 1978 working as a lecturer in orthopaedic surgery until 1990. During this period he completed a masters degree and the RCVS Diploma in Small Animal Orthopaedics. He was appointed as Senior Lecturer and Director of the Queen Mother Hospital for Animals at the Royal Veterinary College from 1991 to 1996. In 1996 he rejoined the University of Glasgow, initially as Director of the Small Animal Hospital, Senior Lecturer in Orthopaedics and then as Professor of Veterinary Clinical Studies and Associate Dean for Clinical Studies from 2006. In 2009 he joined Vets Now Ltd. as National Hospital Director. He joined Fitzpatrick Referrals in Feb 2012 and is currently Managing Director of FitzClinic Ltd (Fitzpatrick Referrals Oncology and Soft Tissue). He is also current Chair of the Board of Trustees of International Cat Care and was appointed to the post of Professor of Veterinary Science at the University of Surrey in 2013. He is an RCVS Diplomate in Orthopaedics and RCVS recognised Specialist. In 2013 he formed a company to develop systems to manage osteoarthritis in animals (AIM.OASYS Ltd.) which is his current research and clinical interest... and passion.

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Early in his professional career Pere held marketing management and marketing research responsibilities in a global pet care corporation. Since 2001 he established as a practice management consultant for veterinary clinics, a task which he has been developing ever since in Spain, Portugal and some Latin American countries. Pere's main professional accomplishments include profitability and pricing research studies involving veterinary clinics, lecturing on practice management in more than 20 countries in Europe, Asia and America, and authoring the textbook "Business Solutions for Veterinary Practices" sold in Spanish and English in more than 10 different countries. In 2008 he co-founded VMS (Veterinary Management Studies), a business intelligence firm that provides a benchmarking service for more than 600 veterinary practices in Spain. Pere is also co-founder and member of the board of the Spanish Veterinary Practice Management Association (AGESVET) and a member of AVPMCA / Vet Partners (American Veterinary Practice Management and Consultants Association).

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David Morgan graduated from Cambridge University Veterinary School (UK) in 1986. He has worked in both large animal and companion animal practice. In 1990 he gained the post-graduate Certificate in Veterinary Radiology. In 1993 he joined P&G Pet Care until the business was acquired by Spectrum Brands on the 1st January 2015. He is the Scientific Communications Senior Manager for Eukanuba and Iams. One of his main interests is how nutrition can help provide support for normal healthy animals as well as how it can be part of a successful management protocol for those with clinical disease.

From perinatal to death – the medical side of ageing

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Introduction

Ageing is defined as 'a time-related deterioration in the physiological functions necessary for survival and fertility' [1] or as 'a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death' [2].

This deterioration of physiological function renders an individual susceptible to many *diseases* such as cancer and heart disease but ageing itself should be carefully distinguished from diseases of ageing which, although important considerations for 'healthy ageing' and subsequent mortality, are not the inevitable consequences of ageing. The characteristics of ageing itself affect all individuals of a species, whereas of course the age-related diseases they suffer differ between individuals.

Why is an internal medicine specialist who researches pancreas and liver diseases in dogs and cats interested in ageing? My particular interest developed as a result of research in chronic diseases of the pancreas and liver associated with progressive fibrosis which are diseases of ageing. My research in polysystemic autoimmune disease in older English cocker spaniels also introduced me to the concept of immunological ageing and how some older-onset immune-mediated diseases in humans and dogs are a result of this ageing in some individuals. These observations led me to consider the complex interaction between a dog's genetic make-up and subsequent environmental stimuli in affecting its longevity and disease risk.

Ultimately, an individual dog's longevity depends on its genetic makeup together with superimposed environmental epigenetic effects throughout its life, starting in utero, together with the superimposed effects of disease which will often accelerate cellular senescence and ageing. In addition, it must not be forgotten that dogs suffer from a cause of death not reported in humans: euthanasia. A dog's human companion may ask for the dog to be put down in old age if they perceive their quality of life as poor. Improved treatment of ageing diseases such as osteoarthritis is also a very important aim in veterinary medicine to improve longevity. A study of canine longevity in Sweden showed a small but significant increase in average numbers of dogs surviving to 10 years comparing dogs studied from 1995-1998 with dogs studied from 1999-2002 (from 64% to 68% respectively) [3]. This increase coincided with an increase in veterinary visits between those two time periods and, importantly, the introduction of non-steroidal anti-inflammatory drugs in to Sweden in 1998, suggesting that increased veterinary care and quality of life was increasing longevity in dogs.

What we as vets are aiming for therefore is not just longevity but a *healthy*, *happy*, old dog.

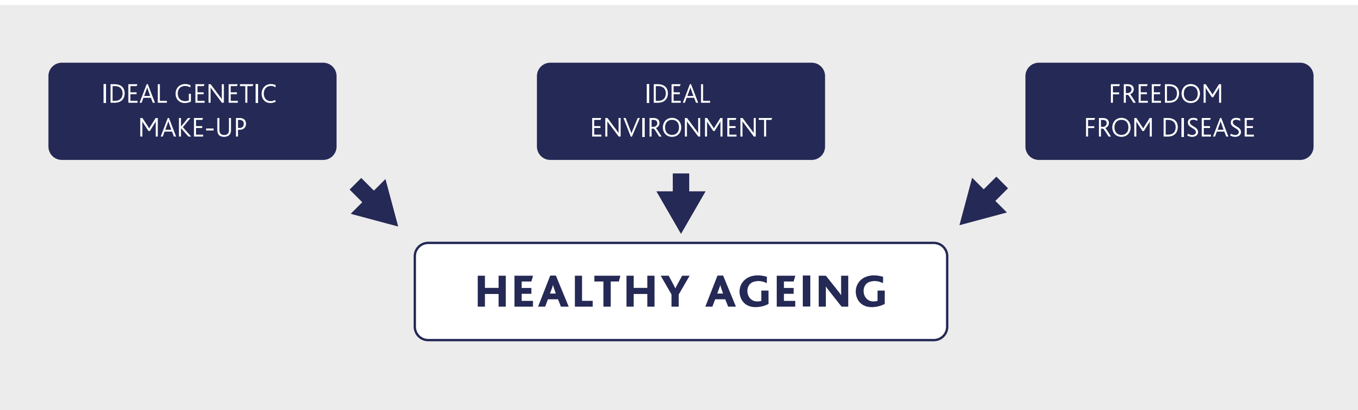

Figure 1. The broad factors leading to healthy ageing in dogs

Figure 2. Many studies have shown that, on average, small breed dogs live longer than large breed dogs

Genetic effects on canine ageing

We all know that ageing and longevity are affected by a complex interaction between genes and environment in all species. Many studies have shown that, in general, large breed dogs have shorter life-spans than small breed dogs in both the USA and Europe [3, 4, 5, 6, 7, 8].

For example, two recent studies in the UK demonstrated similar results: Adams et al in 2010 published the results of a large number of questionnaires sent out to owners of 169 Kennel Club registered breeds. The median age at death of all dogs was 11 years 3 months and 40% of the variability of age at death could be explained by bodyweight. To take two examples from their study, Australian Silky Terriers lived a median of 14.25 years whereas Bernese Mountain dogs lived a median of 8 years. Other data from a large practice-based epidemiological tool (VetCompass) with data from 102,609 dogs of which there were 5095 confirmed deaths showed that the longest-lived breeds were the Miniature Poodle, Bearded Collie, Border Collie and Miniature Dachshund, while the shortest-lived were the Dogue de Bordeaux and Great Dane [7]. Furthermore, it has very recently been shown that the higher the degree of inbreeding in a particular pure-breed dog, the shorter its life expectancy [9]. A dog's genetic make-up therefore undoubtedly has a large effect on its longevity.

These studies raise more questions:

1. Why do small breeds live longer (on average) than larger breeds?
2. If bodyweight (and presumably therefore breed) accounts for 40% of the variability in age at death, what accounts for the other 60%?
3. And is there anything we can do by nutritional and life-style intervention to change the longevity of a particular dog of a particular breed?

Studies are beginning to untangle some of the differences between dog breeds which might help to explain the reasons why their longevity varies, and many of these reasons resonate with the 9 hall marks of ageing listed below. For example, one study showed that there was a positive link between higher energy expenditure in smaller breed dogs and longer life expectancy [10] – contrary to the usual observations in between species studies, where higher energy expenditures tend to be associated with shorter life expectancies, but similar to other intra-species studies. Changes in metabolism and deregulated nutrient sensing have been implicated as one of the hallmarks of ageing providing a clue as to why differences in energy expenditure might impact on longevity [2].

What are the Hallmarks of ageing?

A recent review in Cell [2] listed nine hallmarks of ageing in mammals some of which we will discuss in more detail:

1. Genomic instability including reduced DNA repair
2. Telomere attrition: humans with shorter telomeres are known to have reduced longevity and in dogs, a study has been published demonstrating an inverse relationship between telomere length and longevity in various dog breeds [11]. There has also been a relatively large research focus on telomeres and cancer in dogs.
3. Epigenetic alterations: these are changes to the function of DNA due to environmental and other effects which are likely to be very important in dogs. They are proposed to be reversible (which is exciting!) and include DNA methylation changes and changes to histones (which are the alkaline proteins which DNA is wrapped around) and chromatin. Many of the environmental influences on ageing are likely to be mediated via epigenetic alterations.
4. Loss of protein homeostasis in the cell
5. Deregulated nutrient sensing : this is also very interesting and relevant to our species and is discussed in more detail further on.

6. Mitochondrial dysfunction and increased reactive oxygen species
7. Cellular senescence: although there is a debate as to whether it is the senescence itself which is a problem, or whether it is reduced clearance of senescent cells by the immune system which is the real hallmark of ageing (see more detail below)
8. Stem cell exhaustion
9. Altered intercellular communication including a proinflammatory phenotype with age known as 'inflammageing'

Environmental effects on ageing

All the studies described earlier, and many more, demonstrate the effect of a dog's genetic make-up on its longevity. Can we make any difference by altering the dog's environment? In other words, is there any evidence that changes in nutrition and life-style can make a difference to life-expectancy, on top of the underlying genetic make up of the dog? The answer is an emphatic 'yes'. There is a lot of evidence for the effect of environment throughout the life span on longevity in humans. There is less evidence in dogs – but the little there is strongly supports the assertion that dogs are subject to similar epigenetic environmental effects as their human companions – and in fact, it is very likely that both are affected in similar ways since they share an environment throughout their lives. Pet dogs share our homes and many aspects of our lifestyle. This is important: recent studies have shown striking similarities in owners' and pets' diet and health issues [12]. Indeed, the authors argued strongly that researchers seeking to understand ageing should study dogs sharing an environment with owners but the author noted: '*Yet the pet dog paradigm in ageing research is nascent; tapping into the potential of this model will add to the existing strengths of conventional model systems*.'

In utero and early nutritional effects on ageing

For many years, it has been recognized in humans that birth weight and growth in the first 1-2 years of life has a profound effect on the risk of subsequent disease in humans. Babies that are born 'small for dates' (ie low birth weight at full term) have an increased risk of coronary heart disease; hypertension and type 2 diabetes in later life. This is termed 'fetal programming' , 'the fetal origins hypothesis' or the 'Barker hypothesis' after David Barker, one of the pioneering investigators [13, 14]. Babies can be born 'small for dates' for a number of reasons: severe maternal undernutrition (ie environmental effects) is one of these, as demonstrated in the many studies of the Dutch famine victims after the second world war [15]. Effects on the placenta are also involved and the subject of research in humans. Studies have also shown that birthweight and placental development have effects on longevity in humans [14, 16]. It has become clear after many studies in humans and other mammals that effects in utero are very important: both maternal nutrition and placental effects. The effects in humans appear to be more marked in boys than girls and there are also ethnic differences [14]. It is intriguing to consider whether the mechanisms of some of these ethnic differences in humans may be mirrored in breed differences in dogs. However, frustratingly, there are NO studies of the effect of birth weight or placental size on the risk of subsequent disease in dogs. It is very likely that there is an effect, and this could be exaggerated by the fact that dogs have litters with multiple puppies – some of which may be malnourished in utero with a smaller placenta than their littermates. There is anecdotal evidence for this effect in dogs: it is a popular idea that the 'runt' of the litter is the most unhealthy. Studies of the effect of the uterine environment on subsequent disease in dogs (and cats) are long overdue. The nutrition and health of the pregnant bitch is likely to have a long-lasting effect on the health and longevity of her puppies.

It is not only birthweight which is important, but also nutrition and growth in early childhood in humans. The theory is that a 'small for dates' baby has been programmed for conditions of nutrient scarcity. If the growing child then has access to an excess of calories, this increases the risk of diseases of obesity. There is plenty of evidence in humans that rapid growth and obesity in childhood increases the risk of metabolic and other disease later in life. There is gathering evidence that this is true in dogs, as well. For example, obesity in early life has been shown to increase the risk of mammary cancer in dogs [17,18]. In addition, calorie restriction in the first year of life and subsequently is one of the most effective ways of prolonging longevity in any species, including dogs as discussed in the next section.

Calorie restriction and ageing

Moderate calorie restriction is one of the most effective ways of increasing longevity in all species in which it has been studied [2, 19]. Clearly, excessive calorie restriction (ie starvation) reduces longevity, so this is an example of the typical 'bell shaped' curve seen for adequacy for many nutrients: too few calories or too many calories reduce life expectancy, with an optimal range in the middle. Studies suggest that a 10–50% reduction in calorie intake below usual ad libitum intake causes a proportionate increase in maximum life span, whereas calorie restriction exceeding 50% typically causes starvation and increases mortality [19]. Okinawa, an island in Japan, has been a focus of longevity research in humans for many years: the residents have a culture of moderate calorie restriction (stopping eating before they are satiated) together with a diet rich in anti-oxidants which are thought to be responsible for their exceptional longevity [20].

Does moderate calorie restriction extend longevity in dogs? Excitingly, there is indeed strong evidence that this is the case, at least in Labrador retrievers. A long term longitudinal study of Labrador retrievers showed a marked effect of calorie restriction on longevity: 48 dogs from 7 litters were paired. One of the pair was fed ad lib and the other dog was restricted to 25% less than its partner. Long term follow-up showed that the pair-restricted dogs lived a median of 1.8 years longer and suffered from less osteoarthritis than their overweight partner [21, 22].

The mechanisms behind the profound effect of moderate calorie restriction on longevity are still poorly understood. However, they seem to involve, at least in part, alterations in the endocrine environment of the animal: particularly growth hormone (GH); insulin-like growth factor 1 (IGF-1) and insulin. It has been shown that a reduction in the function of the IGF1, GH or insulin receptor increases longevity [2]. Perhaps paradoxically, GH and IGF-1 are also lower in older dogs and humans. However, these two opposing observations (reductions in IGF1 and GH as a sign of ageing or as a protective mechanism against ageing) can be unified in a hypothesis that down-modulation of these hormones is a defensive response in an older dog aimed at minimizing cell growth in the context of cellular damage, whereas dogs with constitutively reduced IGf1, insulin and GH function can live longer precisely because they have lower rates of cell growth and metabolism [2].

Senescence, immune system ageing and the effect of disease on ageing

As dogs, and humans, age, many changes occur resulting in increasing numbers of senescent cells in organs. Cellular senescence is an ageing change and there is an enormous amount of research on the factors involved in cellular senescence. Senescence has a very specific meaning: a senescent cell is not a 'dead cell' but in fact is a cell which has entered a very stable form of cell cycle arrest that limits the ability of the cell to proliferate [23]. Senescent cells are distinct from quiescent cells; quiescent, but not senescent cells, resume proliferation in response to appropriate signals. In contrast, senescent cells are unresponsive to stimuli to proliferate, but remain metabolically active and have a distinct pro-inflammatory secretory pattern. Senescence is triggered by a broad range of stresses and is a protective change during ageing: senescence is recognized as being protective against cancer – 'damaged' cells can be moved into an arrested state and then removed by the immune system. Arguably, therefore, it is not senescence itself which contributes to ageing, but reduced clearance of senescent cells by the immune system [2].

However, it is becoming clear, at least in humans, that cellular senescence is strongly related to prognosis in inflammatory liver diseases. Markers of cellular senescence in histological sections of liver correlate more strongly with prognosis than any other markers in humans with non-alcoholic fatty liver disease [24] and with alcoholic liver disease [25] and cellular senescence was also correlated with fibrosis in individuals with alcoholic liver disease [25]. Similar studies have yet to be performed in dogs but it seems very likely that chronic inflammatory diseases of the liver and other organs in dogs as well as humans increase cellular senescence and that this is one mechanism by which diseases of older individuals accelerate their ageing.

One area where senescence is very important to ageing is in the immune system: many changes occur during aging which together are termed 'immunosenescence'. At the same time, there is an increase in pro-inflammatory cytokines with aging termed 'inflammageing' which is at least in part due to the fact that senescent cells are secretory and produce pro-inflammatory cytokines [2, 26]. Studies undertaken to date show striking similarities in inflammageing and immunosenescence in dogs and humans [27]. These include alterations in the balance of peripheral blood lymphocyte subpopulations, changes in serum and mucosal immunoglobulin concentrations and the function of phagocytic cells. There are also indications that aged dogs respond less effectively to primary vaccination, while retaining long-term memory of vaccinal immune responses generated as puppies [27].

Autoimmune IgG4+ chronic pancreatitis is an autoimmune disease of older humans and we have described it in older cocker spaniels in the UK. Autoimmune diseases which are commoner in older people such as IgG4 related disease, primary biliary cirrhosis, systemic sclerosis and Sjogren's syndrome are proposed to be caused by an interaction between the environment and immunosenescence. One of a number of features of immunosenescence is thymic degeneration and the accumulation of autoreactive T-cells. In humans, total numbers of T cells do not decline with age but there are changes in T-cell receptors with decreased CD28 expression in both CD4 and CD8+ lymphocytes. All T cells in the placenta express CD28 but there is a gradual reduction with age and this reduction is correlated with a reduced immune response to pathogens and vaccines with age. There is also a suggestion that chronic inflammatory disease results in premature immunosenescence and increased CD28 negative cells. Studies of immunosenescence in dogs are limited, but there is large scope here for more studies of the interaction between dog breeds, immunosenescence and the environment in the cause and progression of chronic inflammatory diseases such as chronic pancreatitis and chronic hepatitis.

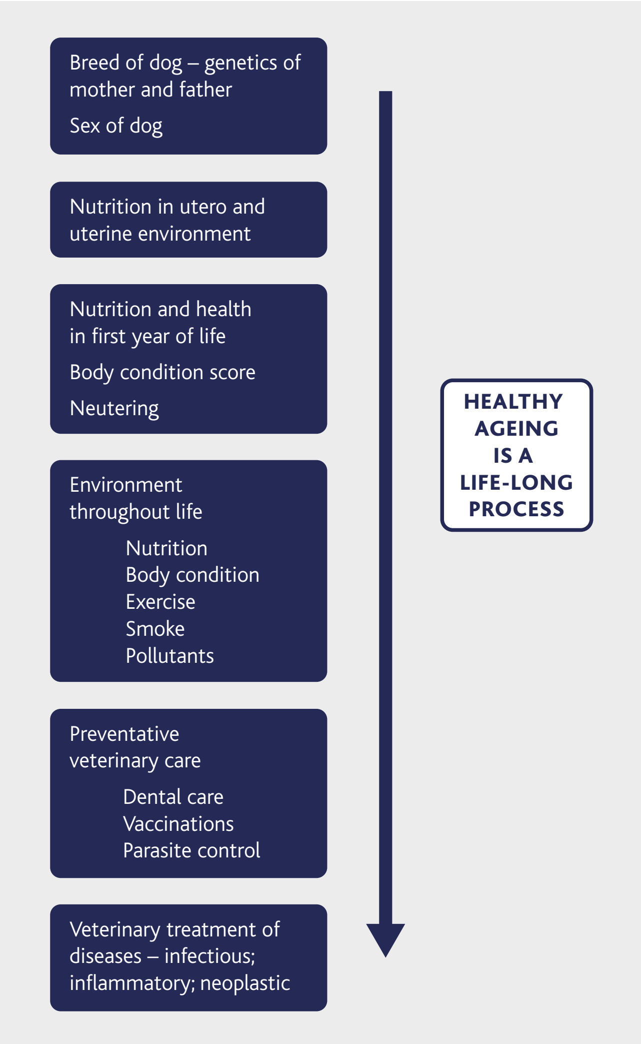

Figure 3. A summary of the many factors involved throughout the life-span which likely impact longevity in dogs

Conclusions

Many factors are involved in ageing and we are only just beginning to unravel these in small animals. Dogs age more quickly than their human counterparts and share an environment with their owners. There are also striking breed differences. Further studies of ageing in dogs should not only be of benefit to the dogs themselves, but also their human companions.

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A multimodal approach to osteoarthritis in growing and ageing dogs

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Introduction

Osteoarthritis is the most common cause of chronic pain in dogs with estimates indicating that 20% of the dog population is affected by the disease [1]. It is also a very common reason for euthanasia in older animals. Fortunately not all animals with pathological changes will show overt clinical signs. Identification of those who are experiencing problems and establishing methods which allow lifelong improvement with control of pain and prolongation of function resulting in improved well-being and longevity represent the major challenges of this disease.

Pain and Osteoarthritis

Osteoarthritis is a progressive degenerative condition eventually involving all of the structures in and around the joint (Fig 1). Degradation of cartilage is a progressive process and in time the joint may become unable to function as a result. However clinical problems that appear are usually the direct result of pain, initiated by the joint pathology. Therefore most of our attempts at managing this disease are aimed primarily at achieving pain control.

At the present time there is no clear method of reversing the pathological process and thus this remains insidiously progressive over a prolonged time interval. Of direct significance to the clinician is the fact that there is very poor correlation seen between both radiographic and pathological state of the problem (Figure 1 and 2) and the extent of pain experienced [2,3]. Clearly individuals who have advanced changes are more likely to experience pain but the amount and extent cannot be derived from these alone. There is growing evidence that many dogs with osteoarthritis may be in a chronic pain state [4]. This is much harder to identify and control than acute pain response in both animals and humans.

Principles for Management

Chronic osteoarthritis is a complex disease that affects and involves multiple systems rather than just cartilage. Traditionally the management of osteoarthritis has been focused on the pathological process within the affected joint, and especially on cartilage. To this end surgical alteration and medical intervention aimed at local anti-inflammatory control and chondroprotection have been the main goals.

In a chronic disease process, like osteoarthritis, we also must look beyond the target organ and try to understand the way the pain experience is processed and, importantly, how it may be modified to the benefit of the patient.

Figure 1. A stifle joint with osteoarthritis showing marginal osteophytes which can be dramatic on radiographs.

Figure 2. A hip radiograph depicting all of the typical changes seen in osteoarthritis, but there is a poor relationship between these changes and pain and function of the animal.

One of the accepted wisdoms in chronic disease is that the pain experience has no protective effect, contrary to acute pain, and is part of the debilitating nature of the disease. By its very nature osteoarthritis is a disease that once initiated persists for the lifespan of the affected patient. As such, all control strategies must take account of this need for long-term treatment. Therefore the objectives for management can be summarised as follows

- Need a strategy that will endure for the life of the patient
- Pain control is key
- Sustaining mobility of both joint and patient is essential for a reasonable lifestyle

Multimodal Management for Osteoarthritis

Achieving satisfactory pain control and maintaining it in the chronic arthritic patient has been shown to be more effective with a more global approach to management than using a single analgesic or anti-inflammatory medical agent [5]. A multimodal approach involves targeting a number of different interventions simultaneously to achieve more effective control as quickly as possible, and then to modify these as the disease progresses or the patients needs change throughout life [6]. It involves therapeutic options, which are neither medical or surgical. Obviously an intervention like this requires careful planning and prioritisation. There are different ways in which this can be established to give a logical approach. Fox [7] has identified six key interventions, all of which are based on evidence of positive effect and can be combined to produce synergism when assembled as a multimodal plan.

This paper outlines a similar method but based on different domains for intervention rather than a specific recipe. This is the 6-point plan (AimOA© System) with six different areas for intervention to form a multimodal approach to any arthritis case. (Table 1).

Using different domains gives more flexibility but still allows a targeted multimodal approach to be followed.

Compliance is essential for this approach to an arthritis problem and the owner must both understand the objectives and be willing to show patience and commitment to achieve benefit. Regular reassessments to ensure improvement are a must.

Planning Osteoarthritis Management

A major problem in arthritis management is considering all of the choices available and selecting an appropriate treatment to meet the clinical objectives. Many attempts at management are based around a single drug strategy. This contradicts the evidence supporting the effectiveness of a multimodal approach suggested above.

Maintenance and Management Plans

One way of ensuring that there is a controlled approach to the problem is by using pre-determined management plans which are customised for each patient. These have the multimodal approach imbedded but require judgements to be made about priorities and sequences of treatments used. They combine pharmacological and non-pharmacological methods and will evolve to meet changing needs in dealing with the chronic disease process. This last point provides sustainability.

Successful plans depend on good clinical assessments being made at different times during the management process. These must be repeatable and allow comparison, not only with the last assessment but also with all assessments recorded. Assessment of a complex disease like osteoarthritis is not an easy feat and is by necessity largely subjective [8,9]. Many attempts have been made to construct a scale that can be used to give repeatable measurements of pain with limited success. Carefully constructed client questionnaires may be the most useful way of judging the subtle changes that can indicate early improvement or deterioration [10,11].

A	Analgesia	NSAIDs; Adjunctive Analgesics
B	Bodyweight and diet	Obesity control; EPA Diet
C	Care	Toxicity monitoring; Practical changes
D	Disease	Chondroprotection; Surgery
E	Exercise and Rehabilitation	Physical Rehab
F	Follow-up	Next appointment

Table 1. AimOA© Multimodal System

Proposed Management Strategy for Osteoarthritis

The **Six Point Plan for OA Management (AimOA© System)** is proposed to satisfy the requirements outlined above. The plan identifies six separate areas of management or modes, which can be addressed simultaneously to deliver a multimodal approach. These areas are identified by prompts A, B, C, D, E, F (Analgesia; Bodyweight and Diet; Care; Disease Exercise and Rehab and Follow –up. Table 1).

Mode A- Analgesia

This is a key mode to management as most animals will present because they are suffering from pain. Medical agents, which have the advantage of producing a rapid alleviation, can achieve early pain control. Agents most commonly used for this purpose are the non-steroidal anti-inflammatory agents. There is a good range available for use in the dog and newer additions to the market have increased options for use[12]. Analgesia can be augmented in a multimodal fashion by the use of adjunctive analgesics like tramadol, the synthetic codeine analogue [13,14], amantidine [15] and gabapentin [14]. Acupuncture has also been used successfully in arthritic cases [16].

Mode B – Bodyweight and Diet

The reduction of obesity is a key target in the management of the disease. There is convincing evidence that controlling bodyweight has a major influence of clinical improvement[17,18,19]. Adipose tissue itself may not be biochemically inactive and has been implicated as a possible inflammatory influence through the action of leptin [20]. Various nutraceutical agents can be considered in this domain. There is increasing evidence that the addition of an EPA rich diet can have a positive influence on the clinical disease [21,22,23]. Special diets formulated with EPA are the easiest way to make this adjustment. All dietary interventions will take a period of time to become effective, EPA for instance, will take 4 weeks before any benefit is seen and this must be considered in the timing and evaluation process.

Mode C – Care

In this domain care applies to being vigilant about intercurrent disease, especially in older patients. Pre-management blood screening may be indicated here especially if medical agents like NSAIDs are going to be used. Monitoring for any toxicity or problems through the management phase is planned in this domain.

The other factors considered here are those of common sense measures to enhance comfort and environmental modifications such as provision of mats on slippery floors or ramps to help getting animals in and out of cars.

Mode D – Disease Modification

Although much of our clinical attention is focused on pain control especially in the early stages of the disease, methods of altering the disease process and pathological changes within the joint must be considered to preserve the function of the joint or the limb. Surgical interventions including joint replacement or modification can be planned here. Medical agents, which influence or modify the structural disease, can also be added in this domain. There is scant evidence for many of the agents, which claim to have disease-modifying effects [24]. Polysulphated glycosaminoglycans, intra-articular visco-substitution with hyaluronic acid and other newer intra-articular techniques such as stem cell therapy and autologous conditioned plasma can be introduced into the plan in this domain.

Controlling and protecting mobility of the joints and ensuring protective muscle function are key counter fibrotic changes in the chronic disease progression.

Mode E – Exercise and Rehabilitation

Great advances are being made in this area and planning here can accelerate recovery and prolong function. This can be as simple as giving precise instruction for controlled exercise (Exercise chart) or could involve sharing care with a rehabilitation specialist. Planning and using a multimodal approach ensures that measures in this domain still complement and are part of the whole approach.

Mode F – Follow –Up

Planning follow-up visits, which allow re-assesment and re-adjustment of the plan are as important as all of the individual interventions. The focus of the plan will need to change with time as the needs of the animal and challenges presented by the disease alter.

Prioritising and Sequencing Management

When setting the first plan certain modes should be identified as a priority depending on the presentation and stage of the disease. The targets for treatment in different phases of the disease progression or recovery can be identified as follows

- Phase 1 - Obvious Pain and/or Obesity
- Phase 2 - Chronic Pain and Mobility Restriction
- Phase 3 – Good quality of life with normal behaviour and free exercise

These phases track the course of the disease from acute needs (Phase 1) to maintenance objectives (Phase 3).

Conclusions

Osteoarthritis is a very complex disease process and as a result presents genuine challenges for management in practices. At present there is not one simple single answer to this problem. Current management advances are being driven by new understanding of the disease and the identification of new tools to control the problem.

Focusing on pain management and developing multimodular programmes that can evolve with the disease problems offer the best chance of successfully managing the clinical problems of chronic osteoarthritis at the present time.

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The role of cancer in canine health and life span. Veterinary oncology in the XXIst century – from chemotherapy to genome

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The importance of veterinary oncology

Veterinary oncology is a growing discipline. There are several compelling reasons and opportunities for this discipline that make us continue our role in the understanding, prevention and elimination or control of this devastating disease. Because cancer is a disease that knows no boundaries between different species, we have a great opportunity to play a key role in comparative oncological medicine, with the ultimate goal of achieving a cure, or in the absence of cure, to transform cancer, which is often an acute problem threatening the patient's life, into a manageable chronic condition.

The number of animals suffering from this disease is growing. One of the reasons is that there are more and more companion animals. For example, according to figures published by the Association of American Feed Control Officials (AAFCO), almost two thirds of the United States households have pets, and in 2008 the estimated number of dogs in the United States was 73 million. Cancer is still one of the main causes of morbidity with at least 4 million dogs developing cancer each year.

The other reason is that owners are increasingly taking care of their pets, through improved prevention plans, better diagnostic methods for the detection of diseases and advances in treatments which allow animals to live longer and healthier lives. People from the United Stated spent about $10,5 billion on their pets' healthcare in 2008. On a worldwide basis, the growth of the pharmaceutical market for companion animals is increasing at rates comparable to that of the human health (http://www.bioportfolio.com).

Prevalence of cancer among our pets

The true prevalence or incidence of cancer in pets is currently unknown. Based on necropsy studies, it has been described that 45% of dogs that live 10 years or more will die of cancer. Without age adjustment, 23% of the patients who had a necropsy died due to cancer. In a survey of the Morris Animal Foundation with over 2,000 respondents, 47% of dog owners said that cancer was the leading cause of death in their pets.

The most cited study remains one that was published 40 years ago. This study analysed the overall rates of cancer incidence in dogs and cats based on a three-year study in veterinary clinics in California between 1963 and 1966. The annual incidence for all types of cancer in dogs was 381/100,000/year. Among the main types of cancer in dogs mammary cancer was, by far, the highest with 198.8/100,000. Skin cancer, not including melanoma, was found in 90.4/100,000 and then several other types of cancer accounted for 20 to 35/100,000.

In a recent study in Europe over a period of 17 years (1984-2002) it was reported that the estimated annual incidence of cancer in dogs is 99.3/100,000 for males and 272.1/100,000 for females. The higher rate of cancer in females (three times higher) was attributed to the high-risk of mammary cancer, accounting for approximately 70% of all cancer types (mammary cancer 191.8/100,000). These findings can most probably be extrapolated to the Spanish patient population.

Risk factors and the most frequent tumours	
Mammary tumours	Obesity, high-fat diet, delayed neutering, certain breeds (Pointer, Poodle, Boston Terrier, Dachshund, German Shepherd, Chihuahua)
Osteosarcoma	Tall breeds and high bodyweight, early neutering, certain breeds (Saint Bernard, Great Danes, Rottweiler, Irish Setter, Doberman, Golden Retriever, Labrador Retriever)
Mastocytoma	Certain breeds (Among other: Boxer, Vizsla, Boston Terrier, Shar-Pei, Labrador Retriever, Golden Retriever)
Lymphoma	Exposure to tobacco smoke, pesticides, certain breeds (Bullmastiff, Boxer, Golden Retriever, Basset Hound, Scottish Terrier)

Adapted from Butler LM, Bonnett BN, Page RL. Epidemiology and the Evidence-Based Medicine Approach. In: Withrow SJ, Vail DM, eds. Withrow and MacEwen's Small Animal Clinical Oncology, 5th ed. St. Louis: Elsevier–Saunders. P 68-82.

Risk factors in veterinary oncology

Several risk factors described in dogs are associated with different types of cancer. Despite the limitations inherent to veterinary studies, several studies have demonstrated that there are reasonable associations.

Based on these risk factors, it could be hypothesized that avoiding some of them such as overweight, sun exposure in white-coated dogs, pesticides exposure, tobacco smoke,… our patients would be less likely to develop cancer and we could prevent it. In one of the few studies looking at cancer prevention it was shown that with high-vegetable diets in Scottish Terriers, the relative risk of developing transitional cell carcinoma of the bladder was reduced.

The owner of a dog with cancer and decision making in veterinary oncology

In human medicine, the ultimate goal of cancer treatments is "to cure" the patient. The combination of different types of treatments (surgery, radiotherapy, etc.) is used in humans as an aggressive therapy to keep people alive as long as possible. In veterinary medicine, there is a general acceptance that euthanasia is a possible choice. Consequently, many animals are not treated, and a large proportion of animals that are treated usually receive less aggressive and more palliative treatments. Although we are still quite far from curing cancer, we increasingly have better therapies (including radiotherapy, immunotherapy or targeted therapies) which not only prolong life, but also allow a better quality of life.

The assessment of the quality of life through questionnaires helps to improve patient care and services we provide. The evaluation of the quality of life can also improve or guide treatment decisions for both the client and the veterinarian. Quality of life is a growing concern for the pet owner and often affects the decision making for a pet with cancer. Most owners are more concerned about the quality of life versus a longer life span and they would prefer better quality of life versus "more time".

Independently of statistics, the perception and reality of the owners support the view that cancer remains the primary concern in their mind concerning pet health and quality of life.

On the other hand, advances in cancer management in human medicine have received much publicity through internet and the media. This publicity has served to educate owners raising the level of expectations regarding therapeutic possibilities, promoting an optimistic atmosphere and a demand for similar care for their pets. The increased longevity in pets, the increased prevalence of cancer and the fact that owners' expectations are higher imply that we must be prepared to respond to these challenges and increased opportunities.

Detect cancer

The detection of cancer by the owner is one of the biggest challenges in treating oncologic patients. The owners who fail to recognize signs of disease in their pets, or do not realize the importance of these signs, often take their pets to the veterinarian at a very late stage.

A study amongst veterinarians has shown that the diagnosis of cancer at an advanced stage often impeded proper management. If pet owners are educated on which signs to look for, cancer could be detected earlier and we can do more for the well-being of patients. The same study

Fig. 1. In Europe we have 2 therapeutic vaccines commercially available for the treatment of melanoma (ONCEPT) and post injection sarcoma in cats (ONCEPT IL-2). Many others are being studied and some have obtained preliminary approval for osteosarcoma and lymphoma.

indicated that most veterinarians tried to find a definitive diagnosis (histopathological) in the vast majority of cancer cases. This large number of veterinarians that are seeking for a definitive diagnosis in cancer cases may reflect advances in understanding of oncology through the development of veterinary oncology as a specialty, a stronger focus on oncology within the university and the increased availability of continuing education courses. This bodes well for the continued successful awareness and understanding of this disease in our pets.

Cancer treatments

In recent years advances in the management of the different types of cancer in pets have benefited from advances in human oncology. Advances in radiotherapy, the chemotherapeutic protocols, administration of targeted drugs (for example tyrosine kinase inhibitor) and the immunotherapy hold great promise for the future of veterinary oncology. Until recently, we had no authorized drugs for the treatment of cancer in our pets on the market, and generally human drugs are used. The arrival of the first vaccine against the malignant melanoma in dogs in 2007 marked a remarkable year for oncological therapy in veterinary medicine. Since then, several vaccines are available on the market or have received preliminary licenses for diseases such as post-injection sarcomas, lymphomas or osteosarcomas (Fig. 1). This new class of therapeutic agents offers a very focused approach to cancer treatment. Immunotherapy is likely to have a very important role over the next 5-10 years, and be at the same level as the classic triad of treatments: surgery, radiotherapy and chemotherapy.

Advances in molecular biology have provided greater understanding about how protein deregulation in tumor cells drives uncontrolled growth and survival of cancer cells. The development of small molecule inhibitors which target these key proteins has transformed cancer therapy in human medicine. The use of these agents also becomes a target in veterinary oncology. This process has been accelerated due to the approval of Toceranib (Palladia, Zoetis) and Mastinib (Masivet® [Europe], Kinavet® [USA], AB Science) a few years ago. However, many challenges still remain; this includes determining how these therapies can be combined effectively with chemotherapy and radiotherapy to reach optimum effectiveness against cancer without increasing toxicity.

A cancer – different results

Cancer refers to a great variety of diseases and, for decades, the experienced pathologist has determined what type of cancer was involved. The classification of the different types of cancer allows us to correlate the tumours of the individual patients with their biological and clinical behaviour. Standard histological approaches and the application of immunohistochemistry are most commonly used to determine the presence of specific markers on the cell surface and subdivide the tumours.

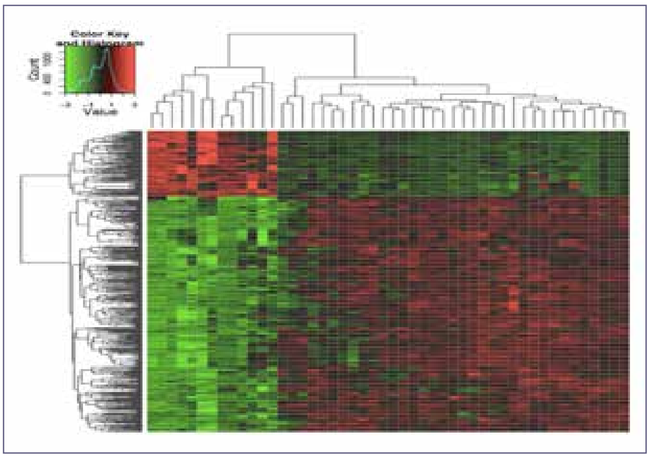

Fig. 2. The discovery of the canine genome has provided the basis for the use of multiple tests such as microarray which give us a huge amount of information about the peculiarities of each tumor and individual patient. Paoloni M, et al. BMC Genomics, 2009.

Since the discovery of the DNA, there has been a global effort to understand how the genome sequences of numerous organisms are related to their health. The study of the human genome was a revolution and, since the launch of the first genome sequencing project only a few years ago, had an enormous impact on human cancer research. In veterinary medicine, the lack of specific molecular and genomic tools for all non-human species has hampered the ability to benefit from this new field. The vision of the genomic leaders recognised the importance of using the comparative analysis of other animals for the sake of our understanding of the human genome. This led in July 2005 to important discoveries such as the sequencing of the canine genome and, later, the sequencing of the feline genome. These discoveries have helped to turn the tide of the canine and feline cancer.

The analysis of the levels of gene expression by microarrays (Fig. 2) with highly specific probes gives us the expression levels of many thousands of genes. Though there are a variety of manufacturing processes for microarrays, the goal is to generate data that highlight deregulated genes in the tissue of interest. The study of gene expression profiles in a large number of human cancers has revealed typical profiles of expression with key clinical characteristics such as a specific subtype of a malignant tumour, the response to a particular therapy, the length of remission and the survival. In the dog, gene expression profiles have been used,

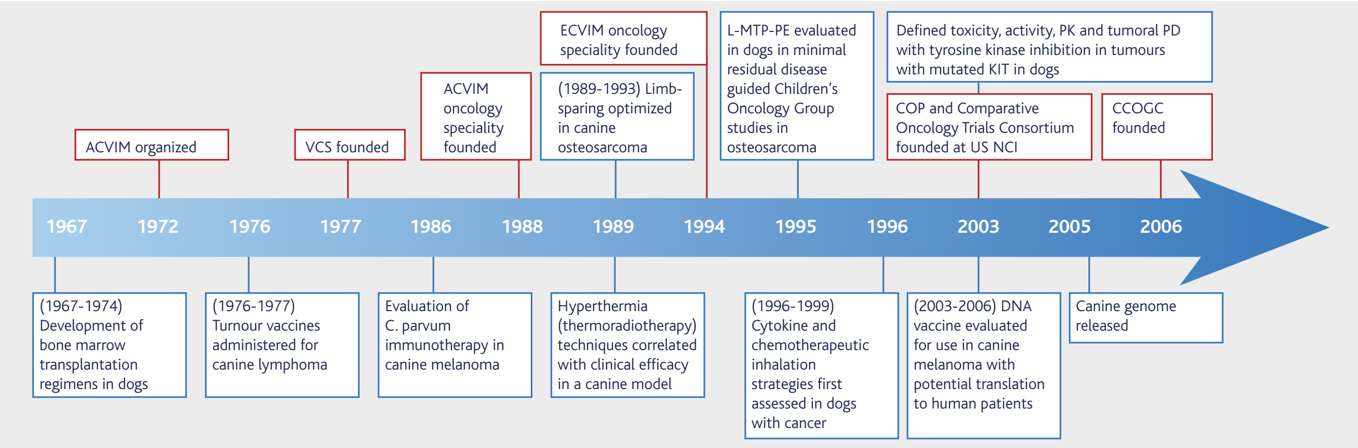

Fig. 3 The comparative oncology gives us a unique opportunity to advance the understanding and development of new treatments in both human and veterinary medicine. Melissa Paoloni & Chand Khanna. Translation of new cancer treatments from pet dogs to humans. Nature Reviews Cancer 8, 2008, 147-156

for example, to reveal genes associated with intracranial tumors and to identify that the high expression of ezrin was associated with the early development of metastasis. These gene expression signatures are now being investigated for their association with the biological behaviour of tumours.

Comparative oncology

Perhaps the greatest opportunity for oncology in this 21st century goes beyond the immediate attention of our patients' and clients' needs. It is the global role we play in advancing the understanding in cancer biology, prevention and treatment from the perspective of comparative oncology. Companion animals spontaneously develop cancer providing us with an excellent opportunity to investigate many aspects of cancer from aetiology to treatment.

One of the most exciting achievements in veterinary oncology in the last decade has been the development of successful groups/partnerships and collaborations to conduct multicenter clinical trials by using biological tumour samples from dogs and cats. These include, among other, the "Consorcio canino de genómica y oncología comparada" (CCOGC, www.ccogc.net). Their success illustrates the growing importance of research in comparative tumour biology. The access to new drugs and biological products will accelerate the clinical application in both species.

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Canine healthy longevity from a practice management perspective

Pere Mercader, Veterinarian and MBA, Director of VMS, Spain

Introduction

Veterinary clinics are facing a tougher environment than ever before: proliferation in the number of veterinary schools and veterinary clinics, increased client price sensitivity due to economic recession, the emerging role of internet as the primary and dominant knowledge source ("Dr.Google effect")...

At the same time, dogs and cats are living longer and better lives. This is due to advances in veterinary medicine coupled with an increased willingness among pet owners to provide the best for their loved friends. Another important factor favouring the canine's population increased longevity is the growing popularity of mixed breed and small breed dogs.

In this complex context, it becomes critical for veterinary practice owners to:

1) Understand the long term demographic trends impacting the pet population. Are the pets they see becoming older? Are they living longer? Are there clear popularity shifts in breed types?
2) Adapt their service offering and their marketing and communication strategies to these trends.

This paper presents the key findings of three separate research projects conducted by VMS (Veterinary Management Studies) with the purpose of bringing light into these relevant matters.

Research methodology

VMS (Veterinary Management Studies) is a quantitative analysis firm specialized in veterinary clinics. The firm captures economic and clinical data from a dynamic panel of over 700 Spanish veterinary practices of different sizes and typologies, spread across the country.

VMS carried three separate but related research projects during 2014:

- Canine Breeds Study [1]: 368.473 canine patient records from 413 veterinary practices were analyzed, with the goal of determining the most popular dog breeds seen by veterinarians, their trends over time (from 2011 to 2014), and their age pyramids.
- Canine Patients Consumption Patterns Study [2]: analysis of consumption patterns of 23.936 canine patients from 88 veterinary practices, with the goal of determining if the pace at which patients generate revenue for the practice increases as they stay longer with the practice.
- Canine Longevity Study [3]: this research calculated the average age at death of 98.060 canine patients which died over the period 2.010 – 2.014 in 401 Spanish veterinary practices, to determine the evolution of canine longevity.

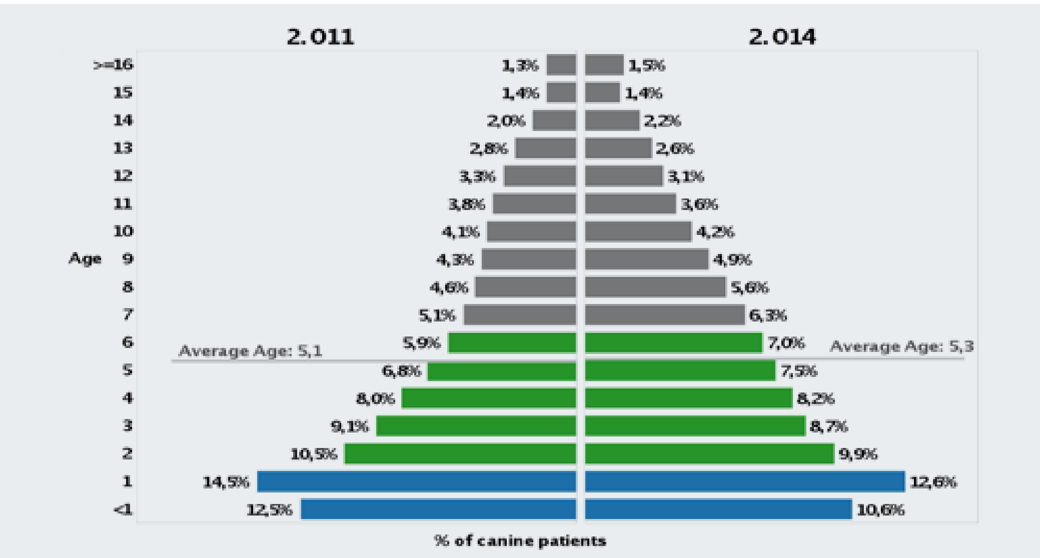

Figure 1. Evolution of age pyramid 2011 – 2014

The key conclusions of these research projects were as follows:

1) The average age of dogs seen by veterinarians is increasing.
2) Senior dogs already account for the largest share of revenue in veterinary clinics.
3) Average longevity of the canine population visiting veterinary practices has increased significantly in the last 5 years. This is true for all breed size groups.
4) Every year a dog stays in the clinic as a patient there is a significant increase in spending, mainly in clinical services due to an increase in the number of transactions.

Practice owners should better be aware of these long term trends and redefine their service offering for senior pets, both from a medical and a client service perspective.

How old are the dogs seen in practice by veterinarians?

Figure 1 (previous page) shows the evolution of the age pyramid (2.011 – 2.014) for 368.473 canine patients from 413 veterinary practices in Spain [1]. Average age of canine patients increased from 5,1 to 5,3 years. The strong economic recession that has affected the Spanish economy in the last 5 years may partially be responsible for these findings (mainly the reduced number of puppies seen by veterinarians).

How relevant are senior (7+) dogs for veterinary practices?

Figure 2 shows the result of an analysis of consumption patterns of 23.936 canine patients from 88 Spanish veterinary practices [2]. Senior dogs are not the dominant age group in number (there are still more adult dogs, between 2 and 7 years old), but they have already become the first group in terms of revenue generation for the practice. Not many veterinarians are aware of this fact. It is still very common to see a dominance of puppy imagery in the marketing and communication materials used by veterinary practices, while senior patients are already taking the lead in revenue generation.

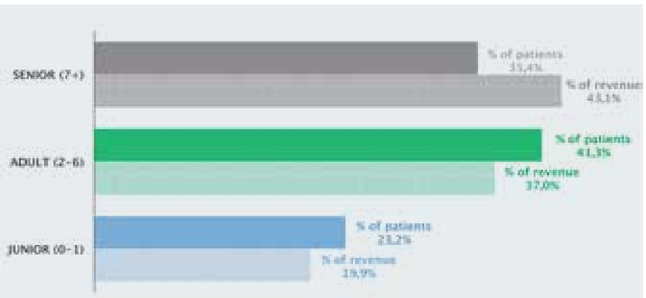

Figure 2. Revenue generation for the practice.

Figure 3. Increase in longevity in all breed groups 2010 – 2014.

Is the longevity of canine patients increasing?

A study of 98.060 canine patients which died over the period 2.010 – 2.014 in 401 Spanish veterinary practices [3] reveals a significant increase in longevity in all breed groups analysed. Figure 3 shows the results. This may be due to improved veterinary care, but also to changes in the popularity of some specific breeds.

Is there an increased spending in the practice as a canine patient stays longer with the clinic?

The patient consumption pattern study conducted by VMS [2] analysed the consumption patterns of 23.936 canine patients from 88 Spanish veterinary clinics. Results were highly conclusive: there is an increased spending pattern which leads to almost tripling the money spent in the practice at the end of the life of the pet. Figure 4 shows the details.

This is due mainly to a combination of two factors:

1) Increased spending over time in clinical services. The consumption in products stays relatively stable through time, but the spending in clinical services experiences a significant increase as the patient stays longer with the practice.

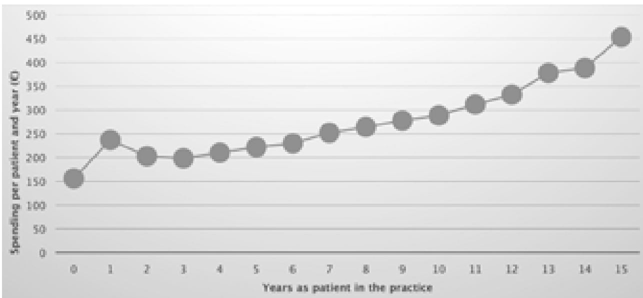

Figure 4. Increased spending pattern at the end of life.

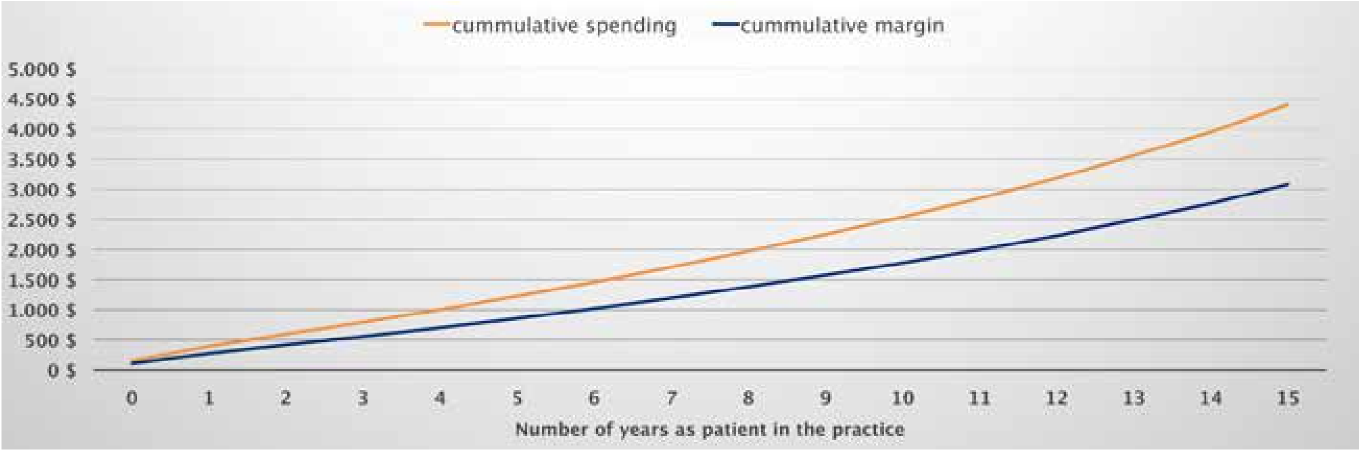

Figure 5. Cumulative revenue of a canine patient during its lifelong relationship.

2) Increased frequency of transactions. Patients spend more on clinical services not because they spend more every time they go to the practice, but rather because they go more often to the practice.

Figure 5 shows the impacting cumulative revenue stream (4.500 euro) generated by a canine patient during its lifelong relationship with a practice, based on the same study. This clearly highlights the critical importance of achieving long-term client loyalty.

Practice management implications

Senior patients are here to stay. They are important in quantity, and in quality. They deserve special care, both from a medical and from a business perspective. There is a significant business opportunity for those practices that innovate in service offering adapted to the specific needs of senior pets. Veterinary practice owners should seriously consider:

- Adapt their existing services to make them more suitable and friendly for senior pets. Could we think of ways to make a consultation, a physical exam, an X-ray, a dental cleaning more *friendly* for a senior pet?
- Incorporate senior pet imagery in their marketing and communication activities. Senior pet owners also like and enjoy seeing pets like theirs... otherwise they may start wondering if they are in the right practice!
- The limit for marketing innovation is unknown: could we think of "senior pet" friendly practices? Or directly "senior pet clinics"? What would happen if one of these opens in town? How would our senior pet clients react?
- Investing in long term loyalty. Quite frequently we focus marketing efforts and resources in capturing new clients. But every time we lose a client (especially in the first years) we say goodbye to a potential revenue stream of thousands of euros... could we think of an increasing reward loyalty scheme (i.e. such as some car insurance companies do) that would encourage our clients to stay with increasing advantages over time?

References

1. VMS breed study, Spain (2014)
2. VMS patient consumption pattern study, Spain (2014)
3. VMS canine longevity study, Spain (2014)

Nutrition's role in healthy ageing and longevity: observations from a 10 year study

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Introduction

A recent UK study showed the longest-lived domestic dogs (*Canis lupus familiaris*) were the Miniature Poodle, Bearded Collie, Border Collie and Miniature Dachshund, and the shortest-lived were the larger Dogue de Bordeaux and Great Dane.[1] But why do we see such a disparity of longevity and mortality amongst the various breeds? When asking this question, the challenge we face is to understand what biological mechanisms underlie the apparent differences among breeds in their ageing rate.[2] In 1996 the heritability of *human* longevity was studied.[3] A total of 2872 pairs of Danish twins were included in this cohort study. The heritability of longevity was estimated to be between 23% (females) and 26% (males). Therefore, longevity in humans seems only to be moderately heritable. The low heritability found is consistent with previous theoretical[4] and animal studies.[5] For our companion animal species we have tended to simply adopt these figures and state that 25% of *canine longevity* is **genetic** with the remaining 75% coming under **environmental** influence in which nutrition plays a pivotal role.

This article will summarise a few key nutritional interventions to consider from a **life course perspective**. That is, interventions that can take place at key points in a dog's life and which could have a beneficial effect on its immediate or future health and its longevity. These 'windows of opportunity' can be in the developing foetus, puppyhood (fig 1), adulthood or in the senior life stage. By no means is this list exhaustive (for further reading see references 6 and 7). Finally, a review will be made on the longevity of a cohort of Labrador Retrievers from a Eukanuba 10+ year feeding study.

No matter our approach, our common goal is to **'add more years to the life of dogs and more life to those years'** and if we can understand the impact of nutrition on healthy ageing and longevity more completely then we can bring this goal even closer for all dogs.

Nutritional Interventions and Healthy Ageing

1) Puppy life stage: skeletal development

Overnutrition, through the excessive intake of calcium and energy, can be harmful for young large and giant breed puppies with a cartilaginous and constant remodeling skeleton.[8] By addressing overnutrition in the critical puppy lifestage our aim is to reduce the incidence of osteoarthritis (OA) in adult

Figure 1. Key nutritional interventions, which can promote healthy ageing and longevity, can be implemented by veterinarians and clients through the entire life of dogs.

	Control Fed *Ad libitum*	Diet Restricted -25 % vs. Control Fed
Number of dogs	24	24
Mean adult body weight	100 %	≈75 %
Mean Body Condition Score (6-12 years) 9 point BCS (ideal = 4-5, too heavy ≥6)	6.7	4.6
Fat mass (6-9 years)	Higher, more constant	Lower, slightly increasing
Median Life span	11.2 years	13.0 years
Incidence and severity of OA	Higher	Lower
Immunological test (4-11 years)	Age-related decline	Slower age-related rate of decline in lymphoproliferative responses to mitogens
Total lymphocytes, T-cells and CD8 cells (4-11 years)	Significant decline over time	No decline

Table 1. Summary of some key observations from two cohorts of Labrador Retrievers either Control Fed (CF) or Diet Restricted (DR).[12-14]

and senior dogs which would be detrimental to their health and potential lifespan (for further information see the text by Professor Carmichael in these proceedings). A study in Great Dane puppies fed from 4-5 weeks onwards with 0.78% calcium ('as fed') in a reduced energy matrix (14.8% fat 'as fed') showed that they had better overall body conformation and better gait analysis than those fed a higher (2.67%) or lower (0.47%) calcium with the same % fat level.[9-11] And, the negative impact of excess energy in growing dogs on their skeletal development has been demonstrated in a lifetime diet restriction study.[12-14] Labrador Retrievers were either fed *ad libitum* (control-fed (CF)) or fed 25% less (diet restriction (DR)) with the same diet. Feeding began at age 8 weeks. Major lifetime observations included delayed onset of late life diseases, especially OA. Among CF dogs at age 2 years, 42% had radiographic evidence of hip OA, compared to 4% among DR dogs. By age 5 years, 52% of CF dogs had radiographic evidence of hip OA, compared to 13% of DR dogs.

Recommendation: controlled level of calcium and energy for optimal growth

Large breed puppies should be weaned onto a nutritional matrix with an appropriately reduced energy density that is linked to a moderate calcium level of ≈0.8% ('as fed'). Puppies should be kept lean throughout their growth period and transitioned onto an adult maintenance diet according to the manufacturers' recommendation. This will help reduce the likelihood of developmental skeletal abnormalities, including osteoarthritis.

2) Adult life stage: maintaining ideal body weight (IBW)

Our main focus is managing the percentage of adipose tissue in the body and avoiding overweight or obesity. Adipose tissue is the only organ in the body that has the potential to increase in mass over the lifetime of the dog. Health problems known to be caused or complicated by obesity include: chronic inflammation, osteoarthritis, pancreatitis, hypertension, pulmonary and cardiovascular disease, insulin resistance, glomerular hyperfiltration, and increased anesthesia-related morbidity and mortality rates.[7] There is also a strong link between calorie intake and ageing: dietary restriction (undernutrition *without* malnutrition) retards the ageing process in laboratory rats and mice.[15] And in dogs, when 48 Labrador Retrievers from 7 litters were assigned to an *ad libitum* control-fed (CF) or diet restricted (DR) fed group (DR group were fed 75% of the amount of food provided to CF group) the mean adult body weights of DR dogs did approximate 75% of those in the CF group over the life time of the dogs, in parallel to food intake (Table 1).[13,14]

Recommendation: maintain an ideal body weight for a longer median lifespan.

Careful control of calorie intake, to try and achieve an IBW over the lifetime of a dog, has been shown to increase median lifespan by 1.8 years.[12-14] Other significant health benefits were noted, ranging from delayed onset of disease, especially OA, to improved immunological responses. Clients should be supported and encouraged to manage their dog's IBW through its *entire* lifespan.

3) Senior life stage: glycaemic control

Glucose metabolism

It has been reported that ageing humans have dysregulated glucose metabolism with an increase in fasting and peak plasma glucose concentrations. This has led to the emergence of the "Glycosylation Theory of Ageing" which states that excess (free) sugars non-enzymatically react with biological proteins to form advanced glycation end (AGE) products.[16] The accumulation of these AGE products have been implicated in contributing to several pathological conditions associated with ageing such as cataracts, atherosclerosis, Alzheimer's disease, and strokes. This decreased ability to manage blood glucose has been noted in older dogs.[17] When comparing young (0.7 years mean age) and old dogs (9.6 years mean age) their glycaemic response was significantly different when fed the same diet. The older dogs had significantly higher blood glucose than the young dogs from 60 to 240 minutes following a glucose tolerance test. And the older dogs' blood glucose remained high even at 240 minutes whereas the young dogs' reached baseline levels by 120 minutes. The glycaemic response can be ameliorated in dogs by choosing a dietary starch source with a low glycaemic index (e.g. barley, maize or sorghum) or augmented with a high glycaemic index source (e.g. rice).[18] When the older dogs (9.6 years mean age) were now fed one of two different diets which had the same total starch content, and only differing with their carbohydrate source, either a low (maize and sorghum) or high (maize, sorghum and rice) glycaemic index matrix, the subsequent glycaemic response showed a significantly higher insulin level from 40 to 180 minutes in dogs fed the high-glycaemic index carbohydrate matrix.[17]

Recommendation: improve the glycaemic response through feeding low GI carbohydrates

Feed a dietary matrix that produces a low glycaemic response through the choice of low glycaemic index (GI) carbohydrates. While it is known that senior dogs have reduced glycaemic control, any dog that is overweight or obese will have reduced insulin sensitivity. Therefore optimal weight control should be extended from the adult life stage through the senior and geriatric life stages alongside the choice of low GI carbohydrates.

Observations from a 10+ year longitudinal feeding study

In July 2004 Eukanuba embarked on a longitudinal study with a cohort of 39 Labrador Retrievers consisting of 12 males and 27 females recruited in early to mid-adulthood, between the ages of 5.37 years and 8.52 years (mean age 6.7 years) to evaluate their health and longevity when continuously fed a Eukanuba-based plane of nutrition. All dogs were neutered and had identical housing, standardised daily care and veterinary care.[19] The daily food allowance for each dog was based on the amount of food needed to maintain each dog within an optimal body condition score (BCS): maintained between 2 and 4 on a 5 point scale (3 = ideal) through adjusting their feeding regimen. Medical conditions were treated by the supervising veterinarian using standard veterinary protocols; however, cancer and severe or life threatening conditions were managed individually by the veterinary care team based on the dog's quality of life assessment. This study was a continuation of efforts to understand the biology of ageing and its valuable application to companion dogs. The average or typical life expectancy of purebred Labrador Retrievers has been reported to range between 10 and 14 years, with a median age of 12.25 to 12.5 years.[1,20] For the present study, an external panel of veterinary and academic experts was convened to independently and objectively define the average lifespan of Labrador Retrievers. After review of the body of evidence, it was the consensus recommendation

Longevity Category		Descriptive statistics for age in years at death/censor date						MST (95% CI) in years from Kaplan-Meier analysis	
		N (%)	Mean	(SD)	Median	(min – max)			
Typical 9 to ≤12.9	Deceased	13 (33%)	12.08*	(1.04)	12.58*	(9.68 – 12.95)		12.44*	(11.70 – 12.80)
Long ≥13 to 15.5	Deceased	15 (39%)	14.21*	(0.58)	14.15*	(13.18 – 15.19)		14.08*	(13.63 – 14.72)
Exceptional ≥15.6	Deceased	6	15.98	(0.49)	15.80	(15.68 – 16.96)			
	Alive†	5	16.82	(0.65)	17.13	(16.04 – 17.50)			
	Sub-total	11 (28%)	16.36*	(0.69)	16.04*	(15.68 – 17.50)		16.47*	(15.76 – NE)
Overall	Overall	39 (100%)	14.11	(1.86)	14.01	(9.68 – 17.50)		14.01	(13.18 – 14.77)

Table 2. Number of dogs, ages at death/censor date† and median survival time (MST) with 95% confidence interval (CI) for the cohort of 39 Labradors. †July 31st 2014. NE = not estimated using Statistix. Within each column (Mean, Median, MST), values which share an asterisk (*) are each significantly different from one another (P < 0.0001) by parametric and non-parametric analysis of variance for age at death/censor date and by Kaplan-Meier survival analysis; values within a column with no asterisk were not compared.

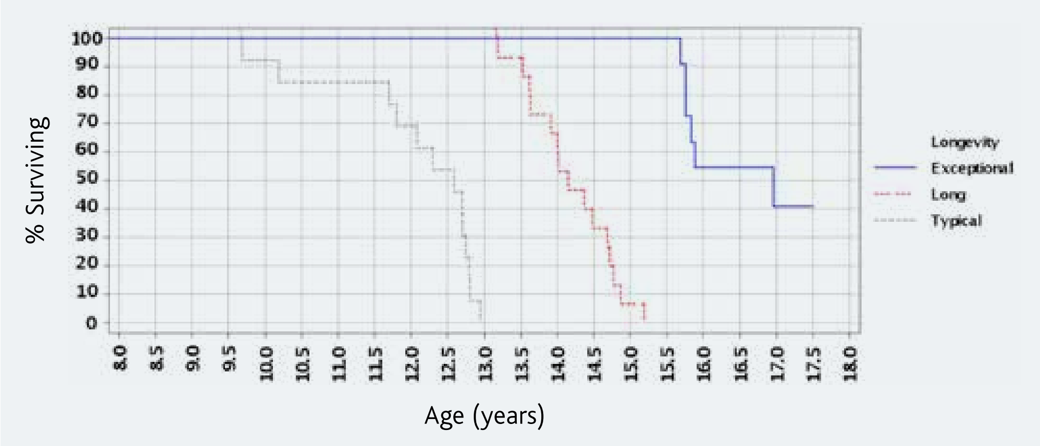

Figure 2. Survival curves for the three lifespan groups, Typical, Long and Exceptional (5 dogs remained alive) as of July 31st 2014.

of the expert panel that the average lifespan of Labrador Retrievers is 12 years. As a result, dogs in this study were classified as 'Typical' when they experienced a lifespan of 9 to ≤12.9 years, 'Long' when they experienced a lifespan between ≥13 and 15.5 years and 'Exceptional' when they achieved ≥15.6 years and beyond. The age of ≥15.6 was selected for the Exceptional lifespan because it corresponds to 30 percent longer[21] than the average lifespan for this breed. Data were analysed using linear mixed models with random effects for both slopes and intercepts and a fixed effect for lifespan grouping variable.

Results and discussion

As of the 31st of July 2014, five dogs remained alive and were classified as exceptionally long lived dogs along with 6 other dogs that reached an exceptional lifespan (n = 11, Table 2, previous page). These five exceptionally long-living dogs continued to be full of life, active, social and highly engaged with their handlers and social groups despite being 16 and 17 years of age. In addition to this a number of independent veterinarians and Labrador Retriever enthusiasts who interacted with these dogs had naturally assumed the dogs to be 3 to 4 years younger than their actual age. Their assumption was based on the overall condition, activity level and interactive behaviour of these dogs despite their advanced age. The remaining dogs were split between the typical lifespan group (n=13) and the long lifespan group (n=15) (Figure 2). Moreover, it can also be reported that a total of 12 dogs lived 25% longer than the average lifespan of Labrador Retrievers by achieving 15 years of age. Significance for the results was set at $P < 0.05$.

A larger proportion of female dogs reached an exceptional age (female:male ratio = 10:1) compared with the typical (7:6) and long (10:5) lifespan groups although this was not statistically significant ($P>0.05$). Using Kaplan-Meier (KM) survival and Cox proportional hazards regression analyses, we found that gender was not significantly associated with survival time (KM $P=0.06$) or risk of death (Cox $P=0.07$). Whilst it has been shown that female Rottweilers were found to have a positive significant association between years of lifetime ovary exposure and longevity, survival analysis did not show an effect of gender or age at neuter on survival for this cohort of 39 dogs. That is, there was no effect of the age of neutering on the risk of death for female dogs (Cox $P=0.2$) or male dogs (Cox $P=0.7$).

Body weight was the only variable that showed a quadratic trend (scatter plot of body weight against time reveals a sloping curve that follows an inverted U shape) so a random

Mean body weight change (kg/dog/year) over time									
Lifespan Group	UP TO 9 YEARS			9 TO 13 YEARS			AFTER 13 YEARS		
	n	mean	SEM	n	mean	SEM	n	mean	SEM
Exceptional (≥ 15.6 y)	11	0.40	0.36	10	0.53*	0.32	10	-1.31	0.74
Long (13 to 15.5 y)	15	0.52	0.28	17	-0.91*	0.28	17	-1.41	0.68
Typical (9 to 12.9 y)	13	0.59	0.30	12	-0.15	0.31	N/A		

Table 3. Mean and standard error of the mean (SEM) body weight change (slope) in kg/dog/year up to 9 years, between 9 and 13 years and after 13 years (y). Means within the 9 to 13 Years column which share an asterisk (*) are significantly different (P =0.007); none of the means within the other two columns (Up to 9 Years, After 13 Years) show any significant difference between them (P > 0.05).

Mean change in body composition (g/dog/year or %) over time									
DXA Variable†	EXCEPTIONAL			LONG			TYPICAL		
	n	mean	SEM	n	mean	SEM	n	mean	SEM
Whole-body total fat (g)	11	625	170	15	320*	152	13	1000*	165
Whole-body total lean (g)	11	-269	165	15	-461	80	13	-593	127
Whole-body fat (%)	11	1.6#	0.4	15	1.3*	0.3	13	2.7*#	0.4
Whole-body lean (%)	11	-1.6#	0.3	15	-1.3*	0.3	13	-2.7*#	0.3
Fat: Lean	11	0.04#	0.01	15	0.03*	0.01	13	0.06*#	0.01
Whole total BMC (g)	11	16.6	3.2	15	18	3.1	13	10	3.2
Whole total BMD (g)	11	0.01#	0.001	15	0.01*	0.001	13	0.01*#	0.001

Table 4. Mean and standard error of the mean (SEM) for change in body composition (slope) as g/dog/year or % up to 13 years. Means within a row that share an asterisk (*) or a hash (#) are significantly different (P < 0.05); means within a row with no asterisk or hash are not significantly different (P > 0.05). †Dual-Energy X-ray Absorptiometer (DXA) (Model Delphi-A, Serial No. 70852; Bedford, MA, USA)

coefficient model was used to compare the slopes of the three groups for body weight changes (kg/dog/year) up to 9 years, 9 to 13 years and changes after 13 years (Table 3). From the start of the study to age 9, body weight increased for all three lifespan groups but the changes over this period were not significantly different. In contrast, there was a significant change in body weight (kg/dog/year) during the span of 9 to 13 years as exceptional dogs increased body weight while the long lifespan dogs lost weight (+0.53 vs. -0.91 respectively). The typical lifespan dogs also lost weight during this period (-0.15) but the loss was not significantly different from the exceptional or long lifespan groups. After age 13, dogs in the exceptional and long groups both lost a comparable amount of body weight.

Dual-Energy X-ray Absorptiometer (DXA) revealed that whole-body fat (g/dog/year) increased in all lifespan groups to age 13 (all three groups' data are included using this age) but the increase was significantly slower only for the long lifespan dogs when compared with typical dogs (P = 0.003) which accumulated fat at 3.1 times the rate over this time period (slopes of +320 vs. +1000, P = 0.003 Table 4). In contrast, all groups lost a similar amount of lean tissue (g/dog/year) through age 13 ranging from -593 (typical) to -269 (exceptional) (P > 0.05). Body fat expressed on a percentage basis (%), increased significantly more slowly to age 13 in both the exceptional and long-lived dogs compared with typical dogs (1.6 and 1.3 vs. 2.7, respectively, P = 0.02 and P = 0.002). Congruently, the loss of whole-body lean (%) through age 13 was significantly slower for dogs of exceptional and long lifespans when compared with those having a typical lifespan (-1.6 and -1.3 vs. -2.7, respectively, P = 0.02 and P = 0.002). Similarly, the change in the fat to lean ratio to age 13 was significantly greater in the typical dogs versus both the exceptional and long lived dogs (P = 0.02 and P = 0.002). Whole-body total bone mineral density (BMD) was significantly lower for typical compared to exceptional and long (P < 0.04). There were no statistically significant differences among the lifespan groups for changes in whole-body total bone mineral content (BMC).

Body mass and body composition (fat to lean ratio) are related to an individual dog's size, but they may also independently influence the rate of ageing and longevity. This was demonstrated in the longitudinal calorie restriction study already mentioned.[12-14] The CR dogs had lower body weight, BCS and body fat and lower serum triglycerides, triiodothyronine, insulin, and glucose concentrations when compared to *ad libitum* control fed dogs. Additionally, these dogs were also less likely to develop cancer, osteoarthritis and liver disease. Any age-related diseases also tended to occur at an older age.

There were no statistically significant differences in BCS slopes over time among the three lifespan groups (data not shown). These results are not surprising because all dogs were managed to maintain a BCS between 2 and 4 over the course of the study. These changes parallel DXA-measured changes in whole-body total fat and whole-body total lean tissue (Table 4). The dogs of exceptional longevity had a slower increase of body fat over time and a slower decrease of lean tissue when compared with dogs that lived a typical lifespan. These differences corroborate those reported in the earlier lifespan study with Labrador Retrievers. Somewhat

	Typical [a]	Long [a]	Exceptional [a]	Diet Restricted [b]
Average daily intake of energy* MJ/d kcal/d	5.88 1405	5.84 1397	5.56 1329	5.15 1230
Energy intake* kcal/kg/d	46.2	46.2	48.0	≈46.5

*Table 5. Energy intake of the three groups of Eukanuba fed dogs[a] as compared to Diet Restricted[b] (DR) dogs fed 25% less than their ad libitum fed pair.[12-14] *metabolic energy of the Eukanuba diet fed was 3669 kcal/kg based on a Modified Atwater calculation.*

paradoxically, dogs in the long-lived group lost weight between the ages of 9 and 13 years, while the exceptionally long-lived dogs maintained or slightly gained weight during this time period. It can be implied from these results that the life-long maintenance of lean body mass and an attenuated accumulation of body fat may be key factors influencing successful ageing and the opportunity to achieve a longer lifespan. Age-related reductions in lean mass, along with high static fat mass have been reported to be strong mortality predictors in the domestic dog.[13,14] A number of age-related changes may contribute to the gradual age-related loss of skeletal muscle. These changes include reduced activity level, loss of motor neurons, decreased protein synthesis, systemic effects of inflammatory mediators and arthritic changes, and chronic disease. These age-related losses of lean tissue likely reflect a culmination of several systemic factors involving one or more common metabolic or genetic pathways.

The benefits of maintaining a body condition as close to ideal as possible needs comment. All three groups of dogs in this recent longitudinal study were maintained as close to their ideal body condition as possible. Table 5 shows a comparison between the Eukanuba fed dogs and those from the diet restricted (DR) study previously mentioned.[12-14] Energy intake per unit of body weight kcal/kg/day for the DR dogs (≈46.5) was very close to those in the Eukanuba study for all three lifespan groups (46.2 to 48). Therefore on an energy intake basis we can consider the DR and Eukanuba fed dogs to be two similar cohorts. However, the oldest dog in the DR study died at 14.5 years of age and in the Eukanuba study it was a female at 17.55 years of age (died mid-August 2014); and, in the DR study, the median lifespan was 13.0 years whilst it was 14.01 years for the Eukanuba dogs.

The benefit of a longitudinal study as reported herein is that researchers are able to detect developments or changes in the characteristics of the target cohort at both the group and the individual level. The key here is that longitudinal studies extend beyond a single moment in time and that they reduce any recall bias. As a result, they can establish sequences of events. Because of this, longitudinal methods are particularly useful when studying development and lifespan issues. There is currently ongoing analysis of the raw data from this 10+ year Eukanuba study and further results using survival analysis techniques to look at how variables change over time will be reported in the future. The long-term objective is to facilitate practical support to veterinarians and dog owners to help further improve the health and longevity of all dogs.

Summary

Ageing is a complex and multi-faceted process that has prompted many new theories in regard to its process and origin. Many studies of ageing have focused on molecular changes across the lifetime of an organism with the reasonable assumption that a series of progressive events collectively contribute to the ageing process. It is probable that there are many dietary factors including total energy intake relative to energy needs (which will determine the risk of obesity), specific nutrients and other non-nutrient bioactive markers, which individually or collectively influence the ageing process. In this latest longitudinal study reported in these proceedings, the combination of a high quality plane of nutrition, appropriate veterinary and husbandry care resulted in 28% of the dogs reaching an exceptional age of ≥15.6 years. All three variables of nutrition, veterinary and husbandry care were kept constant for all dogs and yet 28% achieved both a healthy and exceptional longevity with almost 90% of these Eukanuba fed dogs exceeding their typical lifespan of 12 years. Our future goal is to review and critically assess the role that key nutritional components have potentially played in promoting healthy ageing and longevity in these Labrador Retrievers so that *all* dogs can live to their full genetic potential.

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Notes

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