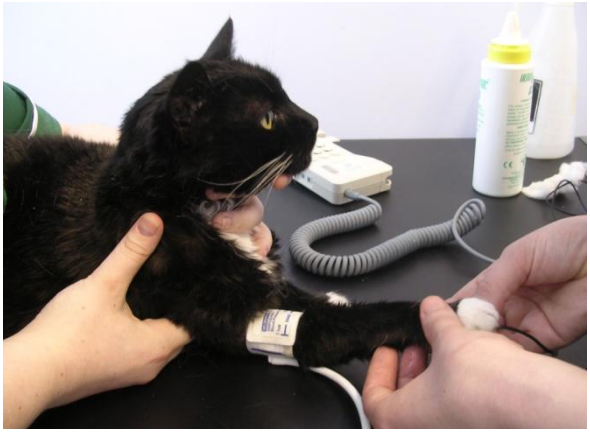
Feline Geriatric Medicine

Mini Series

Session One: Old or ill? Improving quality of life in geriatric felines

Ellie Mardell VetMB, MA, CertSAM, DSAM(Feline), MRCVS
RCVS Specialist in Feline Medicine



Old or Ill? Maintaining quality of life in geriatric cats

With increasing interest in preventative medicine and pro-active screening for disease, geriatric care forms a significant sector of companion animal medicine. Early detection of diseases provides the best opportunity to intervene early which will help maintain quality, if not improve length of, life. Owners need to be counselled in what aspects to look for in their cat that may indicate disease, rather than accepting that alterations to activity levels, appetite, demeanour and personal care are merely "aging changes" that cannot be addressed. As veterinarians we too need to be aware of the best way to question owners in order to maximise historical information, as cats will not always display obvious signs of disease in a way that may be more familiar and easily appreciated in dogs. Various consensus statements aimed at optimising the treatment of certain geriatric illnesses have recently been recently published, addressing chronic kidney disease, diabetes mellitus, osteoarthritis, hyperthyroidism and hypertension. We owe our patients the best care, and in the author's opinion this equates to seeking to cure where possible. Where this is not possible or not feasible, the condition should be managed to the best of our ability. Where all of our management strategies fail or lead to only partial improvement in patient status, we must find ways to support the patient, and to support the owner in difficult decisions including when to euthanase their pet.

Chronic kidney disease and hypertension

Chronic kidney disease (CKD) is a progressive, inflammatory and degenerative condition leading to loss of functional nephrons, reduced glomerular filtration rate (GFR) and inability to produce fully concentrated urine. The main pathological lesion is tubulointerstitial inflammation. Adaptive mechanisms occur, mainly, activation of the renin-angiotensin-aldosterone system (RAAS), causing constriction of the glomerular efferent arteriole. Initially this serves to preserve the GFR of each remaining functional nephron, but with time and advancing disease, the adaptive processes themselves become harmful. The underlying cause of CKD in most cases remains unclear, although conditions such as polycystic kidney disease, pyelonephritis, hypoxia, are known to have the potential to initiate CKD, and a recent study showed an association between dental disease or frequent vaccination and the development of CKD.

Naturally there is a desire to discover factors which may predict the development of CKD, or detect it in its pre-azotaemic stage, and also to identify factors that may be involved in the perpetuation of the condition. The latter would be ideal therapeutic targets. Some studies have identified certain factors associated with a better or poorer prognosis of patients with established CKD. For example, anaemia, altered phosphorous balance, low albumin, proteinuria, later stage of CKD, and low urine specific gravity have all been shown to be associated with a poorer prognosis. However it is unclear, for some or all of these factors, whether they are merely markers of disease severity or whether they mediate disease progression.

Prescribing a "renal" diet is still the single most effective treatment for lengthening (more than doubling) the lifespan of cats with CKD, and reducing negative consequences such as uraemic crises. Renal diets are reduced in phosphate and protein, contain high quality highly digestible protein, are buffered to help counteract acidosis, and are supplemented in B vitamins and potassium. In one study, a diet rich in omega-3 fatty acids performed particularly well[11]. Hyperphosphataemia is associated with a poorer prognosis and the clinical benefits of protein and phosphorous restriction in CKD have been demonstrated. Phosphorus retention, reduced vitamin D activation and elevated parathyroid hormone levels in CKD are important factors in the development of feline mineral and bone disorder (previously termed renal secondary hyperparathyroidism) which has a negative impact on quality of life. Serum phosphate levels are initially maintained within the normal range by increasing levels of parathyroid hormone; dietary phosphate restriction should therefore begin in advance of rising serum phosphate levels. Target phosphate levels for stage 1 and 2 CKD patients

are actually below or in the low end of the standard phosphate reference range (see IRIS recommendations). If diet alone is ineffective, oral phosphate binders can be added in.

It is considered likely that proteinuria is a mediator of feline CKD progression, as has been demonstrated in man and in dogs. Proteinuria is related to intraglomerular pressures, which are typically raised even in the absence of systemic hypertension, due to activation of the intra-renal RAAS at a microvascular level. Proteinuria is undeniably a prognostic factor, with survival being proportional to the degree of proteinuria. Given this and the suspicion that it is a mediator of disease progression, it has become one of our major therapeutic targets. The level of proteinuria at which intervention is advised has been the subject of debate. Feline CKD patients with a UPCR >1 have the poorest prognosis, and benefit the most from control of proteinuria. A UPCR >0.4 is also associated with a greater chance of death and was previously seen as the trigger for instituting therapy. However, a UPCR between 0.2 and 0.4 can be nearly as detrimental as >0.4 , suggesting that therapy should be considered when the UPCR is >0.2. Despite this, convincing evidence that effective control of proteinuria in CKD either prolongs life or slows disease progression, is still lacking.

Options for control of glomerular proteinuria include angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). The mechanism of action is incompletely understood, but is partly due to the inhibition of preferential efferent arteriolar constriction that occurs due to adaptive/maladaptive RAAS activation and increased angiotensin II production, as ACEi prevent the conversion of angiotensin I to angiotensin II. This reduces intra-glomerular pressure, and therefore glomerular damage and resultant proteinuria. Angiotensin II acts upon AT-1 and AT-2 receptors. ACEi block both receptors. ARBs selectively block the AT 1 receptor which is responsible for mediating the undesirable effects of angiotensin II, i.e. vasoconstriction, proteinuria, glomerular hypertrophy, fibrosis, aldosterone release and sodium and water retention. The AT 2 receptor is not blocked and this leaves the potentially beneficial actions of angiotensin II (vasodilation, sodium and water excretion, tissue regeneration) to continue uninhibited. Also, in humans, a phenomenon of “ACE-escape” is frequently seen in proteinuric patients who take ACEi’s long term, where after some months, up-regulation of other enzymes and pathways leads to the production of angiotensin II by other routes, and therefore the recurrence of proteinuria. Whether ACE-escape occurs in feline patients is yet to be established, but should this be the case, ARBs may be of benefit.

Systemic hypertension is a common finding in feline CKD, and it is a cause of proteinuria. A healthy kidney regulates blood pressure, and systemic hypertension is as an indication of renal dysfunction (be it primary or secondary) even in the absence of azotaemia. Blood pressure should be assessed in all cats with CKD, using a Doppler device. Aggressive management of hypertension is warranted; uncontrolled hypertension may contribute to progressive renal disease, and also the consequences of hypertension (particularly blindness) have some of the greatest impacts on quality of life of the patient.

Currently the only licenced product for the control of systemic hypertension in cats is amlodipine (calcium channel blocker). The International Society of Feline Medicine and Surgery has produced a consensus statement which outlines the recommendations for blood pressure measurement and control of hypertension in cats and highlighting the role of amlodipine in the effective control of hypertension (Taylor et al 2017). However there has also been some more recent work suggesting that the ARB telmisartan may have a greater effect on blood pressure than previously assumed.

A chewable form of amlodipine has been shown to be effective in reducing the blood pressure by an average of just over 20mmHg in mildly hypertensive cats (Huhtinen et al 2015). Clinical experience might suggest the drug is capable of a much more powerful effect in cats with more severe hypertension. Telmisartan is currently licenced for use in cats to control proteinuria in cats with CKD. Telmisartan administered at a dose rate on 2mg/kg q 24 hours has been shown to reduce blood pressure significantly in cats with naturally occurring, mild hypertension, regardless of cause but

including cats with CKD (average blood pressure reduction 25 mmHg after one month) (Glaus et al 2017).

As well as regulating water balance and excreting endogenous and exogenous toxins, the healthy kidney regulates blood pressure and acid-base balance, produces erythropoietin and activates vitamin D. All of these functions will be adversely affected by CKD. Patients with CKD should be regularly reviewed, a careful history taken to identify events which may indicate nausea (e.g., reduced appetite, vomiting), and assessment carried out of bodyweight, hydration status, systolic blood pressure, urinalysis (for proteinuria and intermittently to check for the development of urinary tract infections) urea, creatinine, haematology/PCV, phosphate, calcium, potassium and ideally acid-base status. In this way various systemic consequences of CKD can be identified and treated, improving quality of life and in the best case, maximising length of life.

Hyperaldosteronism

Primary hyperaldosteronism is probably under-recognised in cats (Djajadiningrat-Laanen et al 2011). PHA results from a spontaneous over production of aldosterone by the zona glomerulosa of the adrenal gland(s). This may be due to an adenoma, a carcinoma, or hyperplasia.

Cats with hyperaldosteronism classically present with signs relating to hypertension, hypokalaemia, or both. Hypokalaemia may cause inappetence, and in PHA not uncommonly becomes severe enough to cause hypokalaemic myopathy, which generally manifests as a ventroflexed neck and/or plantigrade stance, but occasionally is more subtle and cause signs such as a shifting lameness because of muscle pain. Hypertension often goes unnoticed until there are target-organ consequences particularly reduced or absent vision, or potentially central nervous system effects.

Aldosterone measurement is indicated in any cat with hypertension or hypokalaemia, once these other conditions have been excluded, and also where PHA is to be considered as a concurrent disease. It is not always easy to differentiate between primary and secondary hyperaldosteronism. In secondary hyperaldosteronism, the hormone becomes elevated secondary to raised renin levels. This most commonly arises to any great extent in chronic kidney disease secondary to reduced renal perfusion. It is well known that hypokalaemia can result from CKD, however long term hypokalaemia can itself lead to nephropathy and resultant azotaemia (interestingly there not usually accompanying hyperphosphataemia), and aldosterone is intensely pro-fibrotic (in the kidneys as well as potentially in other organs) thus confounding the diagnosis of PHA versus CKD as the primary condition. Furthermore, given that CKD is common in the aging feline population, it may not be unusual to encounter individuals with both PHA and CKD as separate concurrent diseases. Whether this situation is grossly under-recognised due to the inherent difficulties in diagnosing the two conditions which are involved in such close interplay, and whether PHA left undiagnosed may cause, exacerbate or progress primary CKD, is the subject of much debate (Javadi et al 2005).

Renin measurements may or may not help in the diagnosis of PHA. CKD patients will have elevated aldosterone because of elevated renin. In contrast the identification of a raised aldosterone, with a sub-normal or low-normal renin, in a hypokalaemic patient, is diagnostic for PHA. However, renin is a labile substance and careful sample handling is required to avoid artefactually low measurements. Also, as normal concentrations are already low, it is an inherent problem that the assay can struggle to differentiate between low and normal levels. It is imperative that measurements of aldosterone, renin and potassium are carried out on a single blood draw for meaningful interpretation. Frequently, renin levels will be firmly within the normal range in the face of a raised aldosterone, even when the final diagnosis is confirmed as PHA. Confounding our understanding of primary and secondary hyperaldosteronism is the recognition that various conditions causing hypertension seem to elevate aldosterone disproportionately to renin; the reasons for this have not been established. This means that renin cannot always be relied upon to identify cases of PHA.

Adrenal ultrasound is useful in the diagnosis and further investigation of PHA. Unilateral adrenal enlargement in a hypokalaemic or hypertensive patient with a raised aldosterone, is an indication of likely PHA due to a unilateral adenoma or carcinoma. In bilateral disease, adenomas may present normal or mildly enlarged adrenals, whereas hyperplastic glands tend to be of a normal size, and this can make diagnosis challenging. Where a carcinoma is suspected, or where surgical adrenalectomy is being considered, thoracic radiographs are indicated as well as abdominal ultrasound, to screen for metastases which do occur although not especially commonly.

Both medical management and surgical removal of a unilateral adrenal mass can be considered in the treatment of PHA. Where unilateral disease is identified, surgery can offer a cure, although the client should be cautioned that should histopathology demonstrate hyperplasia or an adenoma, the condition can occasionally recur at a later date in the contralateral gland. Surgery is also not without its risks, mainly fatal haemorrhage and post-operative adrenal insufficiency until the contralateral gland recovers function. Medical therapy may require early stabilisation with potassium supplemented fluids, before switching to oral potassium supplementation. Specific chronic therapy consists of the competitive inhibitor of aldosterone, spironolactone, which helps to maintain potassium levels and control hypertension, and frequently also the calcium channel blocker amlodipine to aid in the control of hypertension which can be severe.

Hyperthyroidism

Hyperthyroidism is the commonest endocrine disorder of cats, and the diagnosis of a feline patient with an over active thyroid is these days routine in general practice. Despite the familiar presentation, our ever increasing appreciation of sequelae such as cardiac disease and hypertension, and possible co-morbid conditions such as chronic kidney disease, make the disease more interesting and increase the complexity of its management.

For the most part, the diagnosis of hyperthyroidism does not present a great challenge. However with an increased prevalence and/or awareness of feline hyperthyroidism, much more subtle or atypical signs relating to the condition may be detected much earlier by either owner or clinician, and these early cases or those compounded by non-thyroidal illness, may present more of a diagnostic challenge.

Thought should be given to the existence of any concurrent medical conditions that the patient may have, as these may influence decisions for management, for example whether general anaesthesia is a reasonable option (for thyroidectomy), or whether significant other disease may influence the patient's overall prognosis (when considering a definitive treatment). In particular the time of diagnosis of hyperthyroidism is a good time to assess baseline cardiac and renal function, and blood pressure, as hyperthyroidism can significantly affect the renal and cardiovascular systems due to an increase in circulating catecholamines and metabolic rate, and a resultant increase in cardiac output. Restoration of a euthyroid state generally improves the cardiovascular status, but careful reassessment is prudent; possibility of a concurrent primary hypertrophic cardiomyopathy, or hypertension due to some other underlying disease, should not be overlooked. In one study just over 20% of cats went on to develop hypertension despite good control of hyperthyroidism over a 6 month period. The cause of this (eg whether it was related to the appearance of chronic kidney disease) is not clear. This contrasts with an earlier study showing that 87% of hyperthyroid cats were hypertensive, but that adequate control of the hyperthyroidism also controlled the hypertension as far as follow-up was maintained (only over 4 months).

Broadly, hyperthyroidism can be cured by surgery, or radioactive iodine treatment, alternatively long term medical management is possible using anti-thyroid drugs or a low iodine diet. Appropriate treatment selection relies on a good understanding of both the disease and its consequences, and the

outcomes of the different treatment options, and should be carefully selected on a case-by-case basis rather than relying on a fall back option of a standard protocol.

The hyperthyroid state increases cardiac output, which increases renal blood flow and therefore glomerular filtration rate (GFR). In addition to monitoring the efficacy of a drug in achieving euthyroidism, repeat assessments of renal function (urea, creatinine and urine specific gravity) are mandatory to detect any renal dysfunction that may become unmasked by the normalisation of GFR that the return to a euthyroid state will achieve. Cats with severe azotaemia once euthyroid, may be better treated long term with anti-thyroid medication (rather than pursuing surgery or radioiodine) such that if necessary a state of mild hyperthyroidism can be deliberately maintained in order to preserve the GFR at an acceptable level, and in particular, iatrogenic hypothyroidism is more easily avoided or corrected. This situation is rare however, and the majority of cats which develop azotaemia once they are euthyroid, have evidence of only mild kidney disease. One study showed that the survival times of this subset of patients is not reduced compared to hyperthyroid cats which remain non-azotaemic once euthyroidism is restored indicating that a treatment with curative intent (surgery or radioiodine) could still be considered.

Response to medical management can help further with the decision over whether or not to pursue a definitive treatment. As a general rule, cats with thyroid adenomas tend to stabilise relatively easily on anti-thyroid medication. Occasional cats (e.g. those with large adenomatous masses or ectopic tissue) may require higher doses of medication than is usually given, but there is still usually a response. In contrast, in the author's experience, cats with carcinomas tend to show a poorer response to anti-thyroid drugs, requiring in some cases very large doses to achieve anywhere near an acceptable level of control. Although this is only a guide rather than an implied diagnosis of carcinoma, it does provides valuable information prior to considering radioiodine (RI) treatment, as "conventional" dose RI will be effective only in cases of thyroid adenoma. In any cases where there is doubt over the cause of the hyperthyroidism, (excisional) biopsy should be considered. Scintigraphy and (ultrasound-guided) fine needle aspirate could be considered as an alternative, however scintigraphy does not reliably differentiate between adenomas and carcinomas, and cytology of thyroid masses can be very challenging to interpret; histopathology is generally preferred.

The anti-thyroid drugs methimazole (also called thiamazole), or carbimazole (which is metabolised to methimazole), can be used to control the hyperthyroid state. These drugs interfere with the synthesis of thyroid hormones by inhibiting the enzyme which incorporates iodine. When monitoring response to therapy, the aim is for the total T4 to sit in the lower half of the reference range. This ensures that control remains adequate despite the daily fluctuations of thyroxine that are expected in all patients. A persistently raised T4 may indicate poor owner or patient compliance, an inadequate dose of medication, or, rapid metabolism of the drug particularly where once-a-day administration of methimazole is being used and the blood sample is drawn (12-)24 hours or more after the tablet was last administered. Occasional cats require a very high dose of anti-thyroid medication to achieve adequate control. As long as side effects do not develop, the dose can be increased as required, even above the datasheet dose range if required, under the cascade.

If the total T4 is below the reference range, it is not always necessary to adjust the dose administered, as cats generally do not show any outward signs of hypothyroidism despite a low TT4 (either they are resistant to the effects of hypothyroidism, or, FT4 or T3 are maintained; this has not been well studied). Occasional patients will demonstrate lethargy, inappetence, weight gain or a greasy, scurfy coat, in conjunction with a low TT4, and in these patients the dose of anti-thyroid drugs is best lowered. Additionally, where iatrogenic hypothyroidism is caused, if the patient also develops azotaemia, a dose-reduction *is* indicated, as this is the very subset of individuals that for whom a reduced survival time (around halved) has been demonstrated. In this study T3 levels were not measured in these cats, but cTSH was and was elevated in nearly 70%, implying genuine hypothyroidism rather than non-thyroidal illness.

Direct side effects of anti thyroid medications are varied. Some can be mild and self limiting such as lethargy, vomiting and anorexia; where this occurs usually temporarily lowering the dose and ensuring administration is with food is enough to resolve the signs. Hepatotoxicity is also well recognised, with hepatic necrosis and intrahepatic cholestasis causing jaundice. This is reversible once the drug is withdrawn.

Blood dyscrasias are rarer but well recognised side effects of anti-thyroid drugs. These are frequently mild and of little significance (e.g. eosinophilia, lymphocytosis). However some abnormalities are more severe and require cessation of the drug, of these, leukopenia and particularly neutropenia is seen most commonly. Thrombocytopenia can occur to the extent that allows spontaneous haemorrhage.

Occasional cats will show profound excoriation of the skin, usually around the face. The condition responds poorly to symptomatic treatment including steroids and always necessitates withdrawal of the drug, after which resolution of the problem usually occurs, although sometimes frustratingly slowly.

Topical methimazole is preferred to oral medication by some owners, and this is now available within the UK. Studies have confirmed efficacy via this route, and with a potentially easier method of administration, compliance would hopefully be improved (but some studies have implied that this is not always the case). The incidence of gastrointestinal side effects is reduced compared to oral anti-thyroid medication, but other side effects occur with the same frequency. The drug is usually applied on the underside of the pinna, so that oral ingestion by the cat should be minimised. In some patients local irritation can occur, and the prior application of a small amount of topical steroid medication can reduce this. Recent studies have indicated that when mixed with some lipophilic carrier molecules, the methimazole may reach the upper side of the ear which could have some safety implications for owners.

Surgical removal of over active thyroid tissue offers a cure for hyperthyroidism. The surgical technique is not especially demanding however tissue handling is important as inadvertent damage to local structures can result in significant post-surgical morbidity. (Horner's, laryngeal paralysis, hypocalcaemia). Hypothyroidism seems to be a rare consequence of thyroidectomy, even bilateral surgery. This is presumably because tiny amounts of normal, atrophied thyroid tissue are left behind and these regenerate and recover function over time.

When a cat that undergoes a planned unilateral thyroidectomy, it must be remembered that in around 70% of cases, the second gland does become overactive in time. Additionally, a problem that has become increasingly recognised over the past few years is the presence of ectopic, usually intra-thoracic, thyroid tissue. This can lead to a failure of a bilateral thyroidectomy to achieve resolution of hyperthyroidism. Such tissue can be removed surgically if the clinician is aware of its presence, and a thoracotomy is not always required if the mass can be reached from the thoracic inlet. Scintigraphy would be the ideal way to assess every hyperthyroid cat pre-operatively, but access to this technique is limited. Medical management or radioactive iodine treatment are suitable alternative therapies for cats with ectopic thyroid tissue.

Radioactive iodine (RI) treatment requires no general anaesthetic, is effective against ectopic thyroid tissue, and there is no risk of post-treatment hypocalcaemia. Response rates are very good, with a cure achieved in 95% cases after a single injection; a further 2-5% cases respond to a second injection. Response is usually achieved by the time the cat is discharged from hospital (generally 2-4 weeks after admission) although occasionally the full effect may not be seen for up to three months. Adenomatous tissue actively concentrates the radioactive iodine, which emits gamma and beta radiation causing cell necrosis within a very small range (2mm), sparing the parathyroid glands. Normal thyroid tissue has atrophied and does not take up the iodine efficiently, so is also protected. However the true incidence of hypothyroidism following radioiodine treatment is not entirely clear.

Many cats may show biochemical hypothyroidism as evidenced by a sub-normal TT4 measurement, however the majority of patients show no signs of hypothyroidism, potentially because T3 levels are maintained, although this has not been well studied. However as discussed above, an association between the development of hypothyroidism and azotaemia, and subsequent shortened survival times, has been demonstrated, and this would preferably be avoided if possible. In this situation supplementation of thyroid hormone is advised, although it is still a matter of opinion when this should be commenced given that recovery of function of remaining normal thyroid tissue may occur over several months following treatment. FT4 and cTSH measurements may be of assistance in decision making. Late recurrence of hyperthyroidism is almost never seen following RI therapy; the treatment includes any subclinically active adenomatous tissue which is presumably a cause of recurrence of hyperthyroidism some months following a unilateral surgery. Late development of hypothyroidism has been documented, unexpectedly.

For radioiodine treatment, patient handling must be kept to a minimum, and hospitalisation periods can be lengthy to allow radioactivity of the patient, their urine and faeces to decay to accepted levels. This type of isolation may be distressing to some cats, and is not always acceptable where prior investigations have identified significant co-morbid disease requiring daily medication or observations.

Hill's y/d diet is a prescription food that is available in the UK for the treatment of hyperthyroid cats with benign disease. The diet is depleted in iodine, depriving the thyroid gland of the element it requires to synthesise the thyroid hormones. y/d is marketed to restore the euthyroid state in hyperthyroid cats, either as a sole treatment or in conjunction with anti-thyroid drugs, although it is presumably particularly useful in patients who are not candidates for a definitive therapy, and have shown side effects on anti-thyroid medication or are non-compliant with the tablets. Because of the thyroid's ability to concentrate any consumed iodine, the diet must be fed as the sole food source to maintain its effect. It is therefore rarely suitable for cats with outdoor access, and it may be difficult to regulate feeding in multi-cat households. The small studies carried out by Hill's did show good results with dietary iodine restriction, varying from partial to complete control, although it should be noted that to reliably establish euthyroidism with a diet containing iodine levels equivalent to that of Hills y/d (0.32 parts per million), it seems the cats in the study had access only to de-ioinsed water. The author's impression is that reactions to the diet are mixed, with its use remaining controversial amongst certain veterinary endocrinologists. Anecdotally, in the clinical setting results seem to vary from good in hyperthyroid cats with mild to moderate elevations in TT4 and where the diet is well accepted as a sole food source, to disappointing where compliance cannot be maintained. Certainly, clients must appreciate that regular monitoring of the patient thyroid levels and general health status must be continued, and a guaranteed efficacy of the diet should not be taken for granted. Also, there are some more recent concerns that the diet contains insufficient protein levels, leading to weight loss if it is fed long term.

Feline degenerative joint disease

Degenerative joint disease (DJD) is common and seen with increasing frequency in aging cat populations. The underlying cause is unclear; one suggestion is repeated microtrauma during jumping. Pathologic changes that occur in osteoarthritis (OA) are; degeneration of the articular cartilages and periarticular tissues, bone remodelling, mild non-suppurative synovial inflammation, and new bone formation at the articular surfaces. Various joints and the spine can be affected signs are rarely overt lameness but more usually decreased activity levels, decreased grooming, difficulty using the litter tray, reduced ability or willingness to jump or climb, and resentment of handling. Cold and damp weather typically exacerbates signs, and discomfort and stiffness will usually be worse after a rest following exercise. Accurate pain assessment in the cat is difficult and there is no standard technique, and the impact on welfare of DJD in elderly cats was probably long underestimated. Joint discomfort, crepitus and/or reduced range of motion may be apparent on examination, but findings will not always correlate well with radiographic changes. These can be marked, and include the presence

of osteophytes, appearing as roughening of the joint surface or more obvious bony spurs, secondary soft tissue swelling, and in advanced cases bone remodelling and sclerosis of subchondral bone. A proactive approach to the diagnosis of DJD is preferable given that overt signs may easily be missed. Careful questioning of the owner as to the cat's demeanour and activity levels may reveal clues indicating the cat is experiencing significant discomfort.

A holistic approach to treatment of OA achieves the best results. The environment can be modified, providing ramps to litter trays and slopes placed over steps, and weight loss is advised in obese cats. Dietary supplementation of omega-3 fatty acids has proven efficacy. Pain relief and control of inflammation is also achieved via the use of NSAIDs. Meloxicam is licensed for use in chronic musculoskeletal disorders, it is palatable, the liquid formulation easy to administer and importantly it is ideal for dose titration. Several studies have demonstrated efficacy and safety in cats, including those with mild CKD. A loading dose of 0.1mg/kg is administered once, followed by a dose of 0.05mg/kg once daily. After a response is seen (usually 5-7 days), it is often possible to reduce the dose further. Often the dose frequency can also be reduced without losing efficacy. Other holistic treatments, such as acupuncture, should not be overlooked as there is gathering objective evidence of efficacy based in physiological responses.

Feline diabetes mellitus

Cats with diabetes mellitus (DM) have a *relative* lack of insulin rather than an absence of production altogether. This means that there is reduced production of the hormone, but also peripheral insensitivity to its actions.

Obesity is a major cause of insulin resistance, as insulin receptors are down regulated and insulin binding is impaired. Glucagon levels increase as the action of insulin on pancreatic alpha-cells is impaired, and this also contributes further to insulin antagonism. White fat is now recognised as an endocrine organ that is in communication with the brain and peripheral tissues. There is a complex interplay of genetic factors and alterations to endocrine function during obesity which results in an increased tendency to DM in certain individuals.

Pancreatitis is another common cause of both reduced insulin production, and insulin resistance. Pancreatitis as a contributory factor in the development or exacerbation of feline DM has probably been under-recognised until recently.

Once insulin resistance occurs, there is a compensatory increase in insulin secretion until the ß-cell islets become exhausted and/or damaged, leading to apoptosis. Bouts of pancreatitis, and amyloid deposition (protein secreted in conjunction with insulin) also reduce ß-cell function. The term "glucose toxicity" refers to the reversible element of this process, where few ß-cells have been lost as yet and although insulin secretion is suppressed, the function can be recovered if the serum glucose is successfully lowered for long enough. There is a window of opportunity where this is most achievable (about 6 months), before irreversible ß-cell damage and loss occurs.

Much emphasis has been placed on the role of diet in diabetic cats, after it was initially demonstrated that high protein and/or low carbohydrate diets improve glycaemic control and increase the chance of diabetic remission. Carbohydrates cause greater insulin release than proteins in all species. Cats are adapted to a high protein diet where glucose production by the liver is continuous, and inherent insulin insensitivity is necessary to maintain blood glucose. The fluctuation in insulin demand created by an influx of carbohydrates is non-physiological. Compared to other species, cats have lower levels of hepatic enzymes designed to metabolise glucose. This and a slower metabolism of glucose to glycogen than non-obligate carnivore species, means that they are already at a disadvantage of glucose tolerance. Providing calories in the form of protein instead, reduces insulin demands, sometimes dramatically.

Insulin choice also affects the chances of diabetic remission. Using the (possibly outdated) goal of successful DM therapy as control of clinical signs without any episodes of hypoglycaemia, conventional medium-acting (lente) insulin given am and pm perform well. However, there is an inevitable period of hyperglycaemia twice daily, when the previous insulin dose has worn off. This is enough to allow ongoing beta-cell damage and suppression; glucose toxicity is not reversed. Under these circumstances, the chances of remission are reduced. Additionally, it is difficult in some cats to alleviate clinical signs to an acceptable extent if twice-daily hyperglycaemia is permitted.

Long acting insulins, such as protamine zinc insulin (PZI), glargine or detemir, prevent these episodes of hyperglycaemia. The greatest chance of remission still requires twice daily administration; this may lead to an overlap effect of each dose, which gives excellent control of clinical signs. Also, the chance of diabetic remission is greatly enhanced when tight glucose control is achieved throughout the 24 hour period, and before ß-cell exhaustion has occurred.

A recent consensus statement from the AAFP and ISFM advocates the use of long acting insulin. ProZinc, a human recombinant PZI insulin produced by Boehringer, is one such preparation which has been available in Canada and the USA for a few years, in Germany since 2014, and has recently become licensed for use in other European countries. Studies have confirmed efficacy, safety and a long duration of action. This insulin is now an attractive alternative to lente insulin in the UK where the prescribing cascade must influence choice of medication.

Cognitive Dysfunction Syndrome (CDS)

It is not recognised that the veterinary species appear to experience consequences of brain aging, in part in a similar manor to people (dementia). Older cats may presented for signs such as pacing, vacant behaviour, vocalisation, restlessness, loss of housetraining, or withdrawn behaviour. It is important first and foremost to seek an underlying cause medical or structural cause where possible. Conditions such as hypertension, diabetes mellitus, and osteoarthritis, can generate signs which will mimic CDS. For example, hypertension can alter mental status, and osteoarthritis may cause a patient to soil in the house or stand staring vacantly if the alternative is to try to find a comfortable sitting or lying pose. CDS has been the subject of increased interest a few years ago, leading to some research into possible causes and efficacy of treatments. It does appear that cerebral atrophy, loss of neurons, purkinje fibres and reduction in cholinergic neurotransmitters, are likely to be in part responsible for the behavioural manifestations seen in the patient. Additionally, of particular interest given the possible role of amyloid in the development of Alzheimer's in people, some aging cat's brains show a haphazard build-up of amyloid beta which may affect cognitive function. Treatment of CDS hinges around both environmental modification and pharmacological intervention. To start with, the environment is enriched and additional stimulation is encouraged for the patient. In the advanced stages the environment should be more restricted, to reduce confusion and increase feelings of security and familiarity. Pheromones such as Feliway can be reassuring. Medical management involves the use of anti-oxidants and omega 3 fatty acids, as early as possible in the course of the disease to reduce ongoing damage within the cerebral tissues. Selegeline may be of benefit in some patients. Controlled studies are few and far between, partly because it is difficult to achieve objective assessment in these patients, and probably partly because any improvement, or, more likely any retardation of deterioration, is slow or subtle. That said, there is some evidence that medication is effective and in particular as there may be individual variation, a proactive approach to treatment should be considered in these cats.

References and further reading

CKD

Boyd LM, Langston C, Thompson K, et al. (2008) Survival in cats with naturally occurring chronic kidney disease (2000–2002). J Vet Intern Med; 22: 1111–1117.

Chakrabarti S, Syme HM, Elliott J. (2012) Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. J Vet Intern Med. Mar-Apr;26(2):275-81

Elliott J, Rawlings JM, Markwell PJ, Barber PJ. (2000) Survival of cats with naturally occurring chronic renal failure: effect of dietary management. J Small Anim Pract. Jun;41(6):235-42

Elliott J, Syme HM. (2006) Proteinuria in chronic kidney disease in cats--prognostic marker or therapeutic target? J Vet Intern Med. Sep-Oct;20(5):1052-3

Finch NC, Syme HM, Elliott J. (2016) Risk Factors for Development of Chronic Kidney Disease in Cats. J Vet Intern Med. Mar;30(2):602-10

Glaus AM, Elliott J and Albrecht B (2017) Efficacy of telmisartan in hypertensive cats: Results of a large European clinical trial (Abstract). In Proceedings of the 27th ECVIM-CA Congress; 2017 Sept 14-16. In: J Vet Intern Med 32;525-609

Huhtinen M, Derré G, Renoldi HJ, Rinkinen M, Adler K, Aspegrén J, Zemirline C, Elliott J. (2015) Randomized placebo-controlled clinical trial of a chewable formulation of amlodipine for the treatment of hypertension in client-owned cats. J Vet Intern Med;29(3):786-93.

King JN, Tasker S, Gunn-Moore DA, et al. (2007) Prognostic factors in cats with chronic kidney disease. *J Vet Intern Med*;21: 906–916.

Ross SJ, Osborne CA, Kirk CA, Lowry SR, Koehler LA, Polzin DJ. (2006) Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. J Am Vet Med Assoc. Sep 15;229(6):949-57

Plantinga EA, Everts H, Kastelein AM, Beynen AC. (2005) Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets. Vet Rec. Aug 3;157(7):185-7

Sent U, Gössl R, Elliott J,Syme HM, and Zimmering T (2015) Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease. Journal of Veterinary Internal Medicine Volume 29; 6, Nov/Dec: 1479–1487

Sparkes AH, Caney S, Chalhoub S, Elliott J, Finch N, Gajanayake I, Langston C, Lefebvre HP, White J, Quimby J. (2016) ISFM Consensus Guidelines on the Diagnosis and Management of Feline Chronic Kidney Disease. J Feline Med Surg. Mar;18(3): 219-39.

Syme HM, Markwell PJ, Pfeiffer D, Elliott J. (2006) Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J Vet Intern Med. May-Jun;20(3):528-35

Osteoarthritis

Bennett D, Zainal Ariffin SM, Johnston P. (2012) Osteoarthritis in the cat: 1. how common is it and how easy to recognise? J Feline Med Surg. Jan;14(1):65-75

Bennett D, Morton C. (2009) A study of owner observed behavioural and lifestyle changes in cats with musculoskeletal disease before and after analgesic therapy. J Feline Med Surg. Dec;11(12):997-1004

Gruen ME, Griffith E, Thomson A, Simpson W, Lascelles BD (2014) Detection of clinically relevant pain relief in cats with degenerative joint disease associated pain. J Vet Intern Med. 2014 Mar-Apr;28(2):346-50

Guillot M, Moreau M, Heit M, Martel-Pelletier J, Pelletier JP, Troncy E. (2013) Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. Vet J. Jun;196(3):360-7

Gunew MN, Menrath VH, Marshall RD. (2008) Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats. J Feline Med Surg. Jul;10(3):235-41

Klinck MP, Frank D, Guillot M, Troncy E. (2012) Owner-perceived signs and veterinary diagnosis in 50 cases of feline osteoarthritis. Can Vet J. 2012 Nov;53(11):1181-6

Lascelles BD, Henry JB 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, Wheeler S, Hansen BD, Zamprogno H, Freire M, Pease A. (2010) Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. Vet Surg. Jul;39(5):535-44

Lascelles BD, DePuy V, Thomson A, Hansen B, Marcellin-Little DJ, Biourge V, Bauer JE. (2010) Evaluation of a therapeutic diet for feline degenerative joint disease. J Vet Intern Med. May-Jun;24(3):487-95

Merola I, Mills DS (2016) Systematic review of the behavioural assessment of pain in cats. J Feline Med Surg. 2016 Feb;18(2):60-76

Sparkes AH, Heiene R, Lascelles BD, Malik R, Sampietro LR, Robertson S, Scherk M, Taylor P; ISFM and AAFP. (2010) ISFM and AAFP consensus guidelines: long-term use of NSAIDs in cats. J Feline Med Surg. 2010 Jul;12(7):521-38

Taylor SS, Sparkes AH, Briscoe K, Carter J, Sala SC, Jepson RE, Reynolds BS, Scansen BA. (2017) ISFM Consensus Guidelines on the Diagnosis and Management of Hypertension in Cats. J Feline Med Surg. 2017 Mar;19(3):288-303.

Hyperthyroidism

Hui TY, Bruyette DS, Moore GE, Scott-Moncrieff JC. (2015) Effect of Feeding an Iodine-Restricted Diet in Cats with Spontaneous Hyperthyroidism. J Vet Intern Med. 2015 Jul-Aug;29(4):1063-8.

Norsworthy GD, Carney HC, Ward CR. (2016) AAFP Guidelines for the Management of Feline Hyperthyroidism. J Feline Med Surg. 2016 Sep;18(9):750.

Peterson ME, Broome MR, Rishniw M (2016). Prevalence and degree of thyroid pathology in hyperthyroid cats increases with disease duration: a cross-sectional analysis of 2096 cats referred for radioiodine therapy. J Feline Med Surg. Feb;18(2):92-103

O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. (2014) Prevalence of disorders recorded in cats attending primary-care veterinary practices in England. Vet J. 2014 Nov;202(2):286-91.

Higgs P, Murray JK, Hibbert A. (2014) Medical management and monitoring of the hyperthyroid cat: a survey of UK general practitioners. J Feline Med Surg. 2014 Oct;16(10):788-95.

Diabetes mellitus

Davison LJ. (2015) Diabetes mellitus and pancreatitis--cause or effect? J Small Anim Pract. 2015 Jan;56(1):50-9

Frank G, Anderson W, Pazak H, Hodgkins E, Ballam J, Laflamme D. (2001) Use of a high-protein diet in the management of feline diabetes mellitus. Vet Ther. 2001 Summer;2(3):238-46.

Mimura K, Mori A, Lee P, Ueda K, Oda H, Saeki K, Arai T, Sako T. (2013) Impact of commercially available diabetic prescription diets on short-term postprandial serum glucose, insulin, triglyceride and free fatty acid concentrations of obese cats. J Vet Med Sci. Jul 31;75(7):929-37

Gostelow R, Forcada Y, Graves T, Church D, Niessen S. (2014)Systematic review of feline diabetic remission: separating fact from opinion. Vet J. Nov;202(2):208-21

Hafner M, Dietiker-Moretti S, Kaufmann K, Mueller C, Lutz TA, Reusch CE, Zini E. (2014) Intensive intravenous infusion of insulin in diabetic cats. J Vet Intern Med. Nov-Dec;28(6):1753-9

Marshall RD, Rand JS, Morton JM. (2008) Glargine and protamine zinc insulin have a longer duration of action and result in lower mean daily glucose concentrations than lente insulin in healthy cats. J Vet PharmacolTher. Jun;31(3):205-12

Nelson RW, Henley K, Cole C, and the PZIR Study Group (2009) Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. J Vet Intern Med ;23 787-793

Sparkes AH, Cannon M, Church D, Fleeman L, Harvey A, Hoenig M, Peterson ME, Reusch CE, Taylor S, Rosenberg D; ISFM. (2015) ISFM consensus guidelines on the practical management of diabetes mellitus in cats. J Feline Med Surg. Mar;17(3):235-50

Other

Ash RA and Harvey AM (2005) Primary hyperaldosteronism in thecat: a series of 13 cases. J Feline Med Surg Jun;7(3):173-82.

Djajadiningrat-Laanen S, Galac S, Kooistra H. (2011) Primary hyperaldosteronism: expanding the diagnostic net. J Feline Med Surg. Sep;13(9):641-50. doi: 10.1016/j.jfms.2011.07.017. Review.

Lo AJ, Holt DE, Brown DC, Schlicksup MD, Orsher RJ, Agnello KA. (2014) Treatment of aldosterone-secreting adrenocortical tumors in cats by unilateral adrenalectomy: 10 cases (2002-2012). J Vet Intern Med. Jan-Feb;28(1):137-43.

Javadi S, Djajadiningrat-Laanen SC, Kooistra HS, van Dongen AM, Voorhout G, van Sluijs FJ, van den Ingh TS, Boer WH, Rijnberk A. (2005) Primary hyperaldosteronism, a mediator of progressive renal disease in cats. Domest Anim Endocrinol. 2005 Jan;28(1):85-104.

Gunn-Moore DA, McVee J, Bradshaw JM, Pearson GR, Head E, Gunn-Moore FJ. (2006) Ageing changes in cat brains demonstrated by beta-amyloid and AT8-immunoreactive phosphorylated tau deposits. J Feline Med Surg. 2006 Aug;8(4):234-42.

Landsberg GM, Nichol J, Araujo JA. (2012) Cognitive dysfunction syndrome: a disease of canine and feline brain aging. Vet Clin North Am Small Anim Pract. 2012 Jul;42(4):749-68, vii.

Landsberg GM, Denenberg S, Araujo JA. (2010) Cognitive dysfunction in cats: a syndrome we used to dismiss as 'old age'. J Feline Med Surg. Nov;12(11):837-48

Pan Y, Araujo JA, Burrows J, de Rivera C, Gore A, Bhatnagar S, Milgram NW. (2013) Cognitive enhancement in middle-aged and old cats with dietary supplementation with a nutrient blend containing fish oil, B vitamins, antioxidants and arginine. Br J Nutr. Jul 14;110(1):40-9.

Vite CH, Head E. (2014) Aging in the canine and feline brain. Vet Clin North Am Small Anim Pract. Nov;44(6):1113-29.