Significance of Signs, Symptoms, mTOR, and Quality of Life

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Abstract

This paper discusses the correlation of objective signs and subjective symptoms with energy level in the patient. Signs, symptoms, and energy level are primarily responsible for vitality and quality of life (QOL). The subjective and observable biomarkers of behavior, energy, appetite, and mood (BEAM), as well as objective biomarkers, can be used by both veterinarians and clients throughout a pet's life to assess and monitor QOL. Patient signs and symptoms can reflect fluctuations in molecular mechanisms of mitochondrial function, energy production, and the molecular biomarker mammalian/mechanistic target of rapamycin (mTOR) that affect patient homeostasis, energy balance, quality of life (QOL), and length of life (LOL). The author postulates that holistically treating patients using BEAM, instead of treating animals with the goal to eliminate individual symptoms, can maintain and improve their QOL and extend LOL.

Abbreviations

BEAM	Behavior, energy, appetite, mood
LOL	Length of life
MPS	Muscle protein synthesis
mTOR	Mechanistic/mammalian target of rapamycin
n-3 PUFA	n-3 polyunsaturated fatty acids
QOL	Quality of life

Introduction

Quality of life (QOL) is important to consider throughout life, but the use of QOL assessments is often limited to patients with serious diseases and to assist with the difficult decision of euthanasia (1, 2). This author suggests that patient lives can be improved and prolonged if, instead of just treating individual symptoms, veterinarians also perform QOL assessments (3). The importance of considering patient QOL increases as life-limiting and serious chronic diseases continue to rise (4–6).

Quality of life (QOL)

For multiple reasons, the ability to measure the quality of life in animals is challenging. The widely accepted World Health Organization definition of QOL for humans is not appropriate for use in domestic species because of its reference to culture and values. The QOL surveys, in addition to being lengthy, cannot be applied directly to veterinary patients because many of the questions are based on the World Health Organization's definition of QOL (7).

For the purpose of this article, the Farm Animal Welfare Council's definition of QOL in relation to the lifestyle of livestock is used, as it is similar to that of companion animal QOL: the ability to live a full life, free of physical, mental, and emotional restrictions, such as pain, senility, and fear (8).

Signs and Symptoms as Biomarkers That Can Be Used to Assess QOL

Behavior, energy, appetite, and mood (BEAM) are 4 symptoms that seem to be clinically sensitive, though not specific, reflections of physiologic homeostasis and QOL (9, 10). BEAM symptoms include behaviors like separation anxiety, fears, phobias, and aggression; cellular energy is reflected by changes in activity, such as getting up to greet people or length of walks; appetite symptoms may present as slower or pickier eating habits; mood, the most subjective part of BEAM, may include the pet spending more time alone or barking more frequently. The same BEAM symptoms may have different underlying causes.

Veterinarians primarily use quantitative biochemical measurements such as blood chemistry parameters as biomarkers that reflect physiologic function. Diagnostic testing of hematocrit, albumin, and serum alkaline phosphatase, for example, are excellent indicators. In addition to allowing evaluation of objective test results, subjective biomarkers such as body condition and BEAM can also be used to assess physiologic function, disease progression, response to treatment, and treatment efficacy, and can inform medical decisions (11, 12). BEAM symptoms are sensitive biomarkers that can indicate internal abnormalities before a specific diagnosis can be made. These subjective symptoms can quickly provide caregivers with information about the energy balance and QOL of their pets (12, 13). As a reflection of the internal balance of the patient, BEAM can be used to monitor and maintain a patient's QOL. Like other biomarkers, BEAM symptoms can change quickly in response to pain or other physiologic fluctuations, like when a previously insatiable pet becomes finicky or skips a meal, and when an ordinarily active pet starts sleeping more or becomes less interactive (14–16).

While client-reported observations, like symptoms and QOL, are viewed as "soft" outcomes by some clinicians and researchers, a growing body of evidence shows that these subjective measures are strong predictors of a patient's response to treatment (17). Clinicians and researchers can improve their diagnostic acumen, provide patients with effective evidence-based symptom management, and make timely QOL interventions when they consider BEAM and other subjective assessments along with conventional objective biomarkers (16).

QOL, Significance of Symptoms, and mTOR

Optimal mitochondrial function and energy production help maintain QOL while maximizing length of life (LOL) (18). Mitochondrial function is associated with an important kinase enzyme, mechanistic/mammalian target of rapamycin (mTOR). The mTOR protein is part of a signaling pathway that affects aging and is associated with canine longevity (19–21). mTOR is associated with function of cellular receptors that sense environmental cues, such as whether a cell is getting sufficient nutrition (22, 23). Chronic diseases associated with disrupted mTOR signaling are increasing, including type 2 diabetes, obesity, metabolic syndrome, and several types of cancer (24). In humans, there is growing evidence to support that energy balance and mTOR play a critical role in the QOL for patients with diseases like cancer (25).

The mTOR gene and the serine/threonine kinase enzyme it codes for are critical for life and are highly evolutionarily conserved (26). The mTOR enzyme helps control cell growth and metabolism, is activated in response to changes in the environment, and positively regulates anabolic processes such as transcription, protein synthesis, and mitochondrial metabolism (26). At the same time, mTOR negatively regulates catabolic processes, such as mRNA degradation, ubiquitin-dependent proteolysis, autophagy, apoptosis, and growth factors like insulin and insulin-like growth factor (27). In good conditions, mTor signals cells to grow and reproduce; in times of stress, it shuts down reproduction and makes cells stress-resistant so they will live longer.

The mTOR pathway is one of the underlying molecular mechanisms that connects energy, symptoms, muscle protein synthesis (MPS), vitality, and QOL by integrating signals from growth factors, nutrients, mutagens, and hormones. For example, upregulation of the mTOR pathway induces cell proliferation and inhibits apoptosis and autophagy (26). Basic research into mTOR and mitochondrial function can be applied to clinical medicine and used to optimize QOL as well as LOL.

Symptoms such as behavior can be indicative of changes in cellular and physiological functions in response to insufficient energy for cellular processes and genetically-

encoded molecular mechanisms (28). For example, in humans, there is a direct relationship between mitochondrial function and chronic fatigue syndrome (29). The symptoms that define QOL are all dependent on the cellular energy required for the optimal function of molecular pathways and organ systems. These processes depend on and consume energy in the form of ATP. The conservation of cellular energy like ATP is an important factor for the maintenance of homeostasis and good QOL in older animals. Frequent client monitoring of symptoms such as BEAM proactively can help QOL and LOL.

Muscle mass and MPS are other important biomarkers controlled by cellular energy and molecular mechanisms (30). Weakness in older patients is often due to sarcopenia secondary to insufficient energy required for the translation of proteins into muscles (31). Energy is critical because the most energy consuming process in the body is the translation of proteins by processes such as MPS (32–34). Other factors that contribute to sarcopenia and require sufficient cellular energy include, but are not limited to, activity level, nutrition, chronic inflammation, DNA damage, elevated oxidative stress, mitochondrial dysfunction, and changes in hormonal milieu (27). Albumin and HCT are biomarkers that reflect alterations in homeostasis and fluctuations of cellular energy; it follows that a decrease in these biomarkers can be associated with sarcopenia (35). These internal biochemical signs can supplement the externally visible, subjective symptom biomarkers such as body condition score to predict early problems and monitor changes over time.

By appreciating the importance of mTOR-associated symptoms and QOL, veterinarians can make appropriate dietary recommendations (26). For example, muscle mass is controlled by MPS; as it decreases with age, mobility may decrease, and frailty increases. Sarcopenia has been shown to significantly decrease QOL of older people (36). In addition to preventing muscle loss by meeting nutritional needs, lifelong conservation of cellular energy by working with already activated molecular mechanisms reduces energy-consuming translation of new proteins to improve physiological function and QOL (32).

Nutritional modifications that affect mTOR, translation, and subsequently sarcopenia include increasing protein intake and nutrients, such as amino acids and fish oils that improve MPS. Other examples of the impact nutrition can have on mTOR activity include the improvement in athletic performance and ATP levels in athletes who eat beets and use supplements, such as omega-3 fatty acids and other polyunsaturated fatty acids. Fish oil-derived n-3 polyunsaturated fatty acids (n-3 PUFA) have been shown to decrease sarcopenia and increase MPS (37). Fish oil supplementation in people results in a detectable increase in skeletal muscle n-3 PUFA that causes positive changes in anabolic signaling molecules like mTOR (37). One potential mechanism of action is that the n-3 PUFA in fish oils enhances mTORC-p70S6K1 phosphorylation (38). It has also been shown that sirtuin-1, which regulates energy efficiency during caloric restriction, inhibits mTOR in dogs and people in response to cellular stress (39, 40). Wasted, debilitated, and sarcopenic patients are just one example of the connection between mTor, symptoms, and QOL.

Medications as Consumers of Cellular Energy

Symptoms of abnormal physiologic function are secondary to disequilibrium often associated with insufficient

energy to maintain equilibrium and normal function. The way that symptoms are treated has a direct effect on internal balance, symptoms, vitality, and QOL. Over the past 60 years, many medical innovations based in genetics and molecular medicine have facilitated the development of pharmaceuticals that target specific molecular mechanisms. Despite this "precision" medicine, over the past 3 decades there has been an increase in the prevalence of several common, yet preventable, diseases among companion animals that mirror the increase of similar diseases in humans (40). The increase of these avoidable common health conditions is of particular concern in dogs and cats because many have a negative effect on QOL (41).

Medications that are used to manipulate physiologic functions often have unintended effects that utilize further cellular energy (42, 43). Cellular energy is decreased when there is opposition to innate molecular mechanisms. Treatments that work against molecular mechanisms cause an increase in disease by increasing internal imbalance and decreasing available energy, vitality, and QOL (44). Treatments that oppose normal function can decrease QOL because while alleviating 1 set of symptoms, they promote other, more chronic ones. For example, this is seen in cases of nephritis secondary to treatment with carprofen after an injury. The production of novel translation products, such as anti-inflammatory proteins, requires additional cellular energy that could be conserved with treatments that work with existing translation products, such as the proteins used during the inflammatory response (45). By definition, anti-pathic treatments work by activating novel enzyme systems that utilize cellular energy for protein synthesis. The longer the duration of drug treatment and the higher the dose, the greater the chance of undesirable effects and problems that lead to prescription of other medications (46). In addition, drug dosing commonly ignores the context of individual variability manifesting as symptoms, or diagnoses, which include factors such as age, organ function, and prior drug adverse effects.

Drugs that target specific processes can be useful in acute situations or to support body functions, such as the use of pimobendan for dogs with heart disease. However, as mentioned previously, cellular energy can be decreased by drugs that activate novel cellular processes and the mTOR system, thereby preventing some patients from getting better with drugs alone. When drug intervention alone fails, vitality and energy-building lifestyle modifications, such as fresher diets and increased exercise, can improve the QOL for many patients.

Signs and symptoms result from the dynamic fluctuation of physiologic processes and the molecular mechanisms that cause them. Maintaining homeostasis is the body's best defense from infection and environmental stress. Medications that modify symptoms may have short-term benefits, but they usually alter self-healing and self-regulating functions in some way (47). In addition, lifestyle errors, such as inadequate diet and prior symptom manipulation, cause a decrease in QOL. To improve health and cure chronic disease, the whole life and its quality must be improved, which probably requires more than drugs.

The author postulates that manipulating symptoms not only lowers cellular energy, but also contributes to the increasing incidence of chronic diseases and cancer. Chronic diseases may be decreased by working with the body, rather than opposing it, by using homeopathy, Ayurveda, or Traditional Chinese Veterinary Medicine (48, 49). The Vitality and Balance System, introduced previously, enables veterinarians to maintain a patient’s dynamic equilibrium and QOL by integrating conventional, physiologic-based veterinary medicine with homeopathy to help the veterinarian preserve a patient’s internal vitality and energy required for wellness and QOL (50).

Energy Conservation, Cancer, BEAM, and QOL

Patients with cancer provide an important example of the association between cellular energy and QOL symptoms. It is well-documented that mitochondrial metabolism and cellular energy, quantifiable with mTOR, play central roles in the development of cancer (47, 49). In addition to their bioenergetic functions, mitochondria participate in processes that are central to the development of cancer, including transcriptional regulation, cell death, and malignant transformation (25).

Treatments that conserve cellular energy can maintain homeostasis and QOL for all patients. However, monitor-

ing and maintaining QOL may be even more important for the patients with advanced cancer, poor prognoses, and decreased LOL. In human medicine, the ratio of expected LOL and QOL is especially important because treatment options, such as chemotherapy and radiotherapy, can increase LOL while decreasing QOL (48, 51). In both human and animal patients, frequent home monitoring of the subjective biomarker BEAM is particularly helpful in guiding treatment-based decisions to maintain QOL, especially since many potentially toxic treatments do not have any evidence-based benefit (52, 53).

Treatments that conserve energy may improve outcomes and prove to be especially useful for cancer patients. Even with very serious and often end-stage diseases, when the expected LOL is short, some patients can fully recover and return to a normal QOL (54). Although this observation remains unexplained, it may be related to individual vitality and energy conservation. The number of these seemingly miraculous recoveries may be increased by a shift in emphasis from symptom elimination treatments to the conservation of cellular energy with monitoring of BEAM, abnormal symptoms, and QOL.

Conclusion

To the authors' knowledge, this is the first report correlating mTOR, cellular energy, symptoms, and QOL. QOL and LOL require conservation of cellular energy. The use of anti-pathic drugs to modify signs and symptoms may be associated with the current trend of increasing chronic disease because they require cellular energy to produce novel translation products (25, 32). Treatments such as homeopathy and Traditional Chinese Veterinary Medicine use less cellular energy because they do not increase the translational production of proteins. Biomarkers like BEAM and mTOR can be used to monitor energy balance and to optimize vitality and QOL throughout life, thus maximizing LOL (41, 48).

The subjective symptom biomarker BEAM is a tool that guardians can use at home to assess their pets' energy balance and QOL. In the author's experience, the holistic approach of monitoring and quantitating BEAM symptoms has been a reliable measure of patient QOL that has helped reduce the fears clients have concerning their pets' symptoms. This approach can be explained to clients simply and easily and makes them more willing to persist patiently with gentle supportive care while their pets heal. When clients understand the meaning of symptoms and monitor BEAM as a reflection of physiologic changes and internal balance, they often choose to avoid eliminating symptoms quickly or harshly. When clients use subjective assessments like BEAM and engage in QOL based decision-making with their veterinarian, their fear of signs and symptoms will decrease and they will tend to be more compliant, and their pets may have better treatment outcomes (55).

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