GHENT UNIVERSITY

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Prophylactic and supportive supplementation of omega-3 fatty acids in diabetic cats

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Promoters:

Veerle Vandendriessche

Prof. Myriam Hesta

Literature review as part of the Master's Dissertation

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Summary

The goal of this thesis is to illustrate the possible importance of omega-3 fatty acid supplementation when confronted with cats that are (at risk of developing) diabetes mellitus. The most common type of diabetes found in cats is diabetes mellitus type 2. Diabetes 2 is associated with risk factors that cause increased insulin resistance from which being obese is the most common and severe one. Diabetic cats are fairly similar to diabetic humans, however development of obesity towards diabetes happens much slower and diabetes type 1 is rarely found in cats. Possible complications in diabetic cats are the development of polyneuropathy, retinopathy, urinary tract infections and secondary renal insufficiency. As a preventative measure, omega-3 fatty acid supplementation works in a variety of ways: it will increase insulin sensitivity, reduce adipose tissue inflammation, improves skeletal muscle metabolic flexibility and also directly decreases metabolic shifts towards obesity. As a supportive measure when already confronted with (type 2) diabetes, supplementation will work towards increasing control on blood lipid and glucose levels as well as preventing or decreasing various complications such as retinopathy, renal insufficiency and vascular dysfunction. Although the possible benefits of omega-3 fatty acid supplementation are clear there are still some risks involved. An example of the possible risks involved would be elevated oxidative stress with an increased need for vitamin E or possible gastro-intestinal distress when the diet is suddenly changed. However the possible benefits do seem to outweigh the risks, thus supplementation may prove beneficial when confronted with diabetic (or obese) cats or, at the very least, more research is definitely to be encouraged.

Key words: diabetes 2, obesity, omega-3 fatty acids, preventative measure, supportive measure.

Dutch summary / Nederlandse samenvatting

Het meest voorkomende type diabetes bij katten is diabetes type 2. Diabetes type 2 ontwikkelt zich bij de kat op een gelijkaardige wijze als bij de mens maar bij de kat blijft de controle over de glucosespiegels in het bloed beter bewaard. Het risico om diabetes type 2 te ontwikkelen wordt sterk verhoogd door de aanwezigheid van een aantal risicofactoren. De belangrijkste risicofactoren zijn de aanwezigheid van een overmaat corticosteroïden, een overmaat groeihormoon, hyperthyroïdie of exogeen toegediende progestagenen (als contraceptie). Hiernaast zijn er ook niet-hormonale factoren van belang en is er ook een polygenetische erfelijke component aanwezig. Veruit de belangrijkste risicofactor is de aanwezigheid van obesitas. Complicaties die veel gezien worden zijn polyneuropathie, retinopathie, een verhoogd risico op urineweginfecties en een risico op het ontstaan van nierinsufficiëntie.

Omega-3 vetzuren zijn een type van poly onverzadigde vetzuren met een onverzadigde koolstofverbinding op de omega-3 locatie in de keten. Sommige van deze vetzuren zoals eicosapentaeenzuur en docosahexaeenzuur vallen onder de categorie van de essentiële vetzuren. Deze vetzuren kunnen door zoogdieren niet of nauwelijks worden aangemaakt en moeten bijgevolg dus vooral uit het voedsel komen. Er is wel een uitzondering bij de kat: in tijden van nood is de kat in staat kleine hoeveelheden docosahexaeenzuur lokaal in de hersenen aan te maken. Bij dit proces vindt de eindstap plaats in de hersenen, maar wordt er eerst een tussenproduct in de lever aangemaakt vanuit alfa-linoleenzuur. Na deze tussenstap kan het benodigde docosahexaeenzuur worden aangemaakt in het hersenweefsel.

Omega-3 supplementatie heeft een positieve werking op het endocanaboïd systeem, hierbij wordt er een shift geïnduceerd naar verhoogde vetverbranding, verminderde eetlust en een verhoogde glucose opname door het spierweefsel. Hiernaast voorkomt omega-3 supplementatie dat de insuline resistentie, die het gevolg is van obesitas, toeneemt door verbeterde werking van de insuline signalering en een afgenomen lokale inflammatie van het vetweefsel. Ook wordt de metabole flexibiliteit van het spierweefsel herstelt, waardoor er een toegenomen controle over de glucose spiegels in het bloed bewerkstelligd wordt. Als laatst dient ook opgemerkt te worden dat ook de ontwikkeling van diabetes type 1 vermoedelijk (deels) kan worden voorkomen door een omega-3 rijk dieet.

Ondanks dat dieren niet veel te maken krijgen met cardiovasculaire problemen zijn er toch een aantal nuttige eigenschappen toe te dichten aan omega-3 supplementatie. Supplementatie verbetert bloed lipide parameters, vertraagt de progressie van diabetes type 2, verbetert de controle over bloed glucose spiegels en reeds aanwezige insuline resistentie wordt getemperd. Omega-6 vetzuren hebben echter een omgekeerd effect op de controle over de bloed glucose spiegels. Ook is er een algeheel positief effect op de oxidatieve stress in het lichaam gemeten, wordt de endotheel functie terug genormaliseerd en wordt retinadegradatie voorkomen door supplementatie. In combinatie met renine angiotensine systeem

inhibitors werkt omega-3 supplementatie ook zeer goed preventief tegen chronische nierschade die kan ontstaan ten gevolge van diabetes type 2.

Ondanks de vele voordelen verbonden aan omega-3 supplementatie zijn er toch een aantal aandachtspunten. Een dieet met een hoog vetgehalte (hier vallen ook onverzadigde vetzuren onder) verhoogd het vetgehalte in de lever, hiernaast is er toch een toegenomen oxidatieve belasting in de spieren en de rest van het lichaam geobserveerd. Vanwege de toegenomen oxidatieve belasting is de behoefte aan vitamine E in het dieet dan ook verhoogd. Hiernaast bevat een dieet rijk aan onverzadigde vetzuren een relatief laag aandeel in vitamine E van nature. Zorg moet dan ook gedragen worden om depletie van vitamine E reserves te voorkomen. Ook moet er zorg worden gedragen dat de verhouding tussen omega-3 en omega-6 vetzuren meer richting omega-3 vetzuren gelegen is. Immers omega-6 heeft veelal een tegengesteld effect aan omega-3. Naast de anti-inflammatoire effecten van omega-3 zijn er ook antitrombotische effecten beschreven door remming van de trombocyten functie. Als laatst dient er ook rekening te worden gehouden met de energetische waarde van het dieet en dient men langzaam over te schakelen om gastro-intestinale complicaties en ongewenste gewichtstoename te voorkomen.

Introduction

In cats diabetes mellitus (mainly diabetes mellitus type 2) is a common disease affecting cats and owners alike worldwide. The treatment of diabetes mellitus consists of insulin injections in combination with a therapeutic diet. Most commonly regular insulin injections with Caninsulin® or glargine (Lantus®) combined with a diet adapted towards diabetic animals is used as treatment. The diet aims at lowering glucose load by having reduced glucose content, a significant amount of fibers present and an increased protein content. The regular insulin injections are given to mimic natural insulin response after meals and to bring down blood glucose levels. However, with the advent of new discoveries about the beneficial effects of omega-3 poly-unsaturated fat supplementation, or in short (omega-3) PUFAS, in humans as well as animals one could raise the question if omega-3 fatty acid supplementation in the diet could prove beneficial. It may be a useful additional supportive measure for the more motivated pet owner or when confronted with insufficient response towards regular therapy. This goes for diabetic cats as well as cats running an increased risk of developing diabetes 2 in the future. This thesis's goal is to shed light on some of the possible benefits and risks associated with omega-3 supplementation in regards to animals coping with diabetes 2 or running an increased risk of developing diabetes 2 in the near future.

Diabetes Mellitus in cats

The most common type of diabetes found in cats is diabetes mellitus type 2 (diabetes 2). Diabetes mellitus type 1 is a rare occurrence in cats (diabetes 1) (Nelson R.W. and Reusch C.E. 2014). Because of the relative rarity of diabetes 1 as opposed to diabetes 2, diabetes 2 will be the main focus of this article.

Insulin resistance is seen as a major risk factor for the development of diabetes 2 in the cat. Common hormonal causes for insulin resistance and/or abnormal insulin response are hyperadrenocorticism, the exogenous administration of progestogens (commonly used for contraception), hyper secretion of growth hormone (as seen in cats with acromegaly) and hyperthyroidism. There are also non-hormonal factors that can cause insulin resistance like (chronic) pancreatitis, heart failure, renal disease and non-endocrine neoplasia (Scott-Moncrieff J.C. 2010).

Other causes like polygenetic factors can play a role too but factors such as level of physical activity, sex, and age are more important (McCann T.M., *et al* 2007). Finally excessive weight in the form of obesity is considered a major risk factor for developing insulin resistance. Studies have shown significantly lower insulin sensitivity when gaining weight (Appleton D.J., *et al* 2001; Hoenig M., *et al* 2007). Because of this obese cats run a substantially higher risk of developing diabetes 2 (Scarlett J.M. and Donoghue S. 1998).

These conclusions are further reinforced by a Swedish study on the national cat population in Sweden. In this study being obese and/or performing low levels of physical activity combined with being fed an energy dense diet were identified as major risk factors. Because of this, the study further proceeded to recommend using this knowledge in preventative measures towards the development of diabetes 2 (Sallander M., *et al* 2012). Indeed a significant amount of the United States veterinary practitioners are already including preventative dietary measures aimed at weight reduction in their treatment of diabetes mellitus. This holds especially true for newly graduated practitioners (Smith J.R., *et al* 2012).

When compared to humans, cats are fairly similar when it comes to diabetes 2. Relative age of onset, association with obesity, island amyloid deposits, loss of beta cell mass and possible complications as a result of type 2 diabetes are very similar between humans and cats. The most notable complications in cats are polyneuropathy and diabetic retinopathy. Polyneuropathy is a complication caused by degeneration of the Schwann cells and degeneration of the neural axons. The symptoms in cats mainly consist of plantigrade stance of the hind limb, reduced patellar reflexes and posterior paresis. Symptoms of diabetic retinopathy consist of a plethora of vascular defects in the retina visible with an ophthalmoscope. Although the pathogenesis of diabetic retinopathy is complicated, the induced retinal hypoxia and this subsequent neovascularization is believed to play a significant role in the development of blindness in cats (Henson M.S. and O'Brien T.D. 2006).

Cats with diabetes 2 also run an increased risk of developing bacterial infections, especially in the urinary tract, as well as developing secondary renal insufficiency (Scott-Moncrieff J.C. 2010).

It should be noted however that although insulin resistance in cats is very similar compared to humans, blood glucose control is maintained far better. The reason for this is that although cats are insulin resistant, the liver is able to maintain sensitivity better and thus glucose output is lowered to compensate for the high blood glucose levels. This causes the development from obesity towards diabetes 2 to be significantly slower in cats compared to humans (Hoenig M. 2012).

Introduction to omega-3 fatty acids in the diet

Omega-3 fatty acids are a type of polyunsaturated fatty acids most commonly found in plant and fish oils of which fish oils are the most concentrated source. Omega-3 fatty acids contain an unsaturated link at the omega-3 carbon position (see figure 1 for reference).

Plant oils mostly contain the omega-3 fatty acid alpha-linolenic acid. Fish oils contain high levels of eicosapentaenoic acid (EPA) as well as docosahexaenoic acid (DHA). EPA and DHA fall under the essential omega-3 fatty acid category. Humans (and most other mammals) do not have the capacity to synthetize these omega-3 fatty acids in useful quantities, hence the name essential fatty acids. Small amounts of alpha-linolenic acid can be converted in EPA or DHA with the help of desaturase enzymes. However, this process isn't as effective a method of acquiring needed EPA and DHA as directly using fatty acids derived from food. This means essential omega-3 fatty acids have to come mostly from our diet (Nettleton J.A. 1991; Nelson D. and Cox M.M. 2008). This need for essential fatty acids being present in the diet holds true for cats as well (Rivers J.P., *et al* 1975).

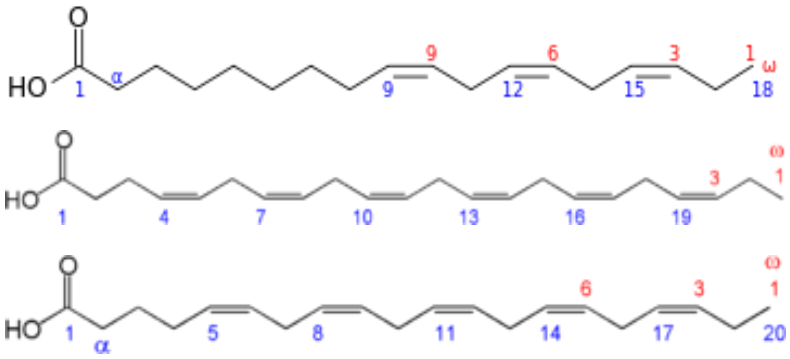

Figure 1. The chemical structure of the omega-3 fatty acids alpha-linolenic acid, DHA and EPA (ordered from top to bottom) (courtesy Wikipedia).

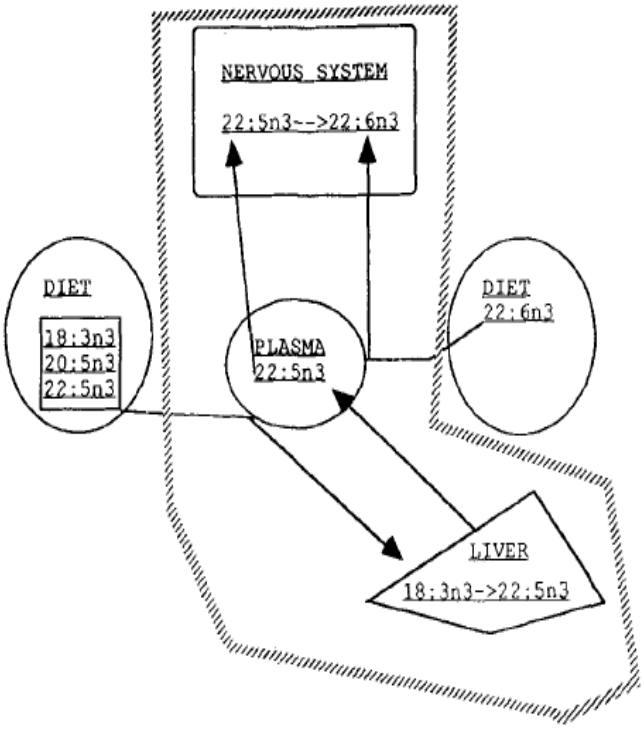

Figure 2. Overview of the conversion of alpha-linolenic (18:3n3) acid to DHA (22:6n3) in the cat (Pawlosky R, et al 1994).

Recently a study discovered evidence that cats may still be able to synthetize some of these needed essential fatty acids from alpha-linolenic acid (or other omega-3

derivatives) in times of need, in contrast to human subjects. This process takes place in the liver where alpha-linolenic acid (18:3n3) is converted into docosapentaenoic acid (22:5n3), locally in the brain docosapentaenoic acid is then converted into DHA (22:6n3) (see figure 2 for reference). This process takes place with the help of various elongase and desaturase enzymes (elongating the chain and desaturating the chain respectively). However the amount of fatty acids synthesized this way are small quantities only (Pawlosky R, *et al* 1994).

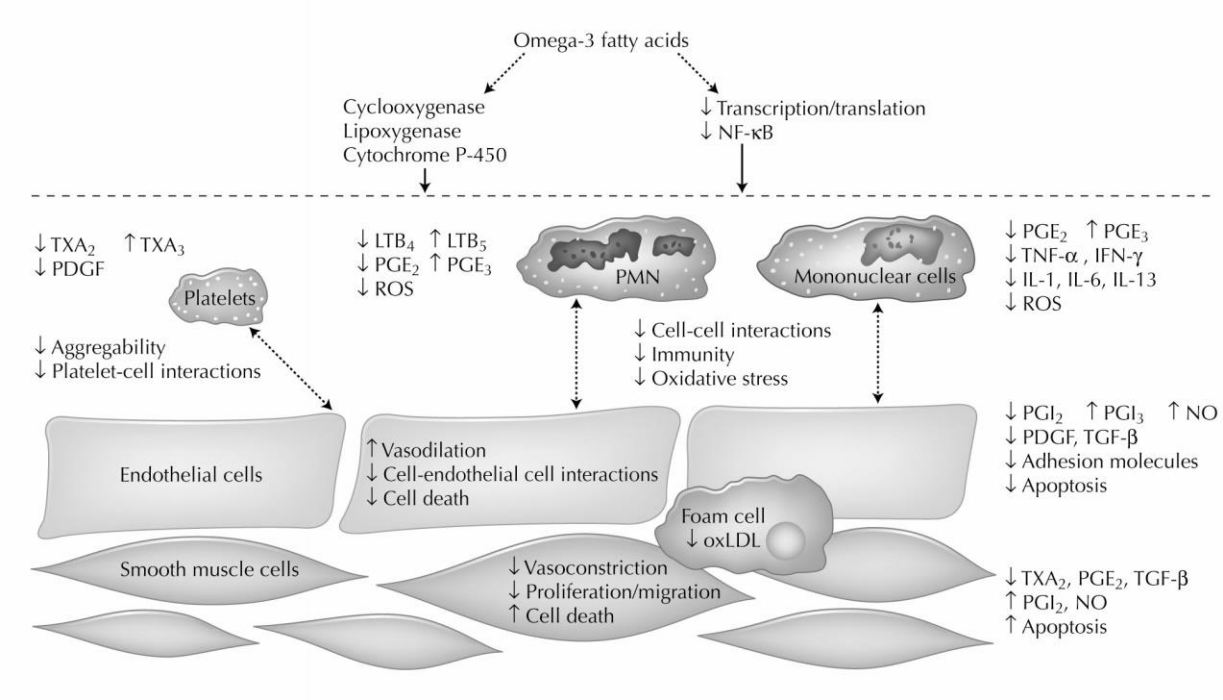

Figure 3. Graphical overview of the various anti-inflammatory actions omega-3 fatty acids perform in the body (Mori T.A. and Beilin L.J. 2004)

Interestingly enough, besides the essential role most of the omega-3 fatty acids play in the normal functioning of the animal, there are also a number of other useful qualities found over the years. For example it is demonstrated that omega-3 fatty acids have a profound anti-inflammatory effect, modulate immune response, dictate some of the platelet function and prevent heart disease in humans (see figure 3 for additional information) (Kris-Etherton P.M., *et al* 2002; Mori T.A. and Beilin L.J. 2004). There are also a number of beneficial effects towards the prevention and treatment of diabetes observed. Those effects will be discussed further along in this article.

Omega-3 fatty acid supplementation as a preventative measure

As discussed in the previous chapter obesity is a major risk factor in the development of type 2 diabetes because of the subsequent induction of insulin resistance. Because of this, it is not surprising the majority of the studied preventative effects of omega-3 fatty acid supplementation are aimed towards counteracting the effects of obesity or preventing obesity entirely.

The classic approach to alleviate problems caused by obesity, are dietary measures aimed towards weight reduction of the patient. However, a relatively new approach towards obesity shows the role of overstimulation of the endocanaboïd system found in the body and a possible way to influence this system. The endocanaboïd system's tone shifts towards increased appetite, reduced glucose uptake in the muscles and increased fat accretion when the diet shifts towards an omega-6 fatty acid rich diet. This contributes towards developing obesity. A dietary shift towards more omega-3 fatty acids will induce a normalization of this system towards a more balanced profile and thus actively plays a role in prevention of further fat accumulation (Kim J., *et al* 2013).

The lowered glucose tolerance and insulin response resulting in the onset of metabolic syndrome and ultimately type 2 diabetes in obese animals, can also be alleviated with omega-3 fatty acid supplementation. PUFA replacement of saturated acids in fatty acid rich diets in obese animals has been demonstrated to normalize glucose tolerance and insulin signaling. However this is mainly observed for omega-3 rich replacements, omega-6 rich replacements only had partial effect (Lamping K.L., *et al* 2013).

Obesity also leads to chronic inflammation of the adipose tissue. This inflammatory process is the result of chronic stressing of adipose cells by ways of nutrient overload. This chronic stress results in the release of pro-inflammatory cytokines (TNF-α and IL-6) and eventually cell death. This in turn attracts macrophages. Normally these macrophages are of a wound healing phenotype that release little to no pro-inflammatory cytokines. In obese subjects, however, they are more like the activated macrophage phenotype. This in turn leads to the release of even more pro-inflammatory cytokines, inhibiting insulin receptor function by targeting kinases involved in their signaling. (Flock M.R., *et al* 2013). An omega-3 fatty acid rich diet alleviates this inflammation and may have a positive effect towards insulin resistance in obese animals (Liu H., *et al* 2013). However actual recommendations towards effective doses and length of treatment cannot be made yet, even in human medicine. This is caused by inconsistent results and a lack of further research (Robinson L.E. and Mazurak V.C. 2013).

The anti-inflammatory effects of omega-3 fatty acid supplementation in the adipose tissues are also demonstrated in a study by Spencer M. *et al* (2013), however actual improvement in insulin response was not measured in this study. This study also concluded higher initial tissue macrophage levels resulted in a larger reduction after supplementation. In summary it was concluded that subjects with higher levels of

inflammation may be benefitting the most when being fed a diet shifted towards a higher omega-3 fatty acid intake (Spencer M., *et al* 2013).

Another field omega-3 fatty acid supplementation influences is at the metabolic level of the skeletal muscle tissue. In an obese body and/or type 2 diabetic body, the metabolic flexibility of the skeletal muscles is decreased. At basal insulin levels in a normal subject the skeletal muscles predominantly use lipid peroxidation for energy generation, however when insulin levels increase there is a switch towards mainly glucose as a fuel. In resistant/obese subjects, basal lipid peroxidation is decreased. At higher insulin levels the switch towards glucose as fuel does not occur but rather lipid peroxidation is increased, thus a form of metabolic inflexibility is the end result. Although at first sight the increase in fatty acid peroxidation will seem like a good thing it actually is not. The end result is an increase in muscle fatty acid accumulation and the inability to adapt to fastening periods as well as periods of high blood glucose levels (Kelley D.E. and Mandarino L.J. 2000). Because the skeletal muscles are a main site in the body for glucose uptake, restoring the metabolic flexibility of skeletal muscle tissue is beneficial for obese and/or insulin resistant subjects. Dietary supplementation of omega-3 fatty acids improves this muscle metabolic flexibility, especially when combined with insulin sensitizing and/or hypolipidemic pharmaceuticals (Horakova O., *et al* 2012).

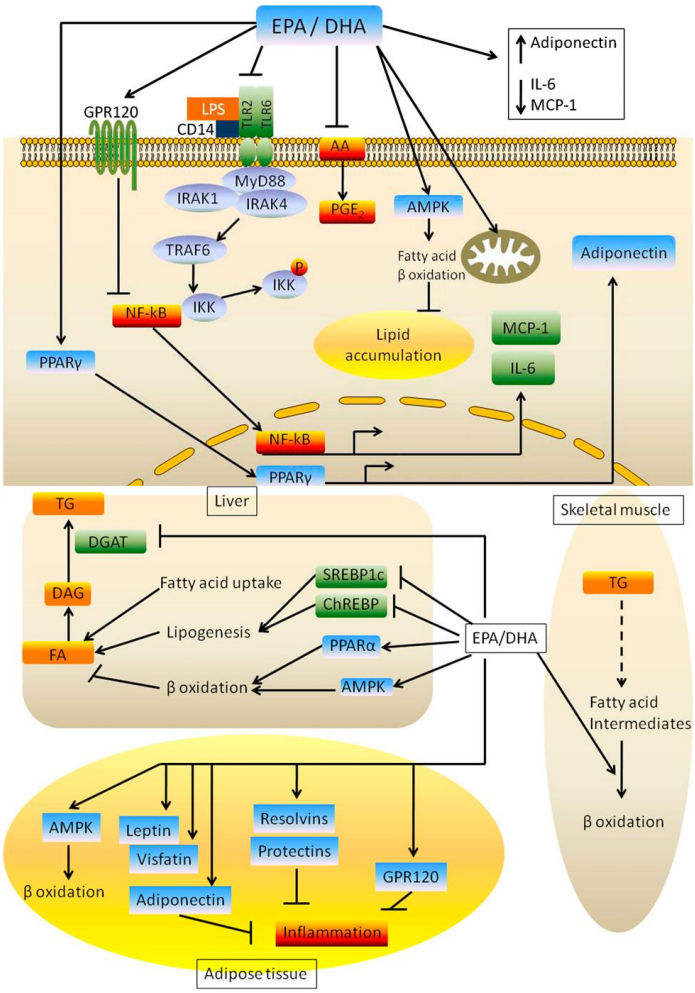

Figure 4. Graphical illustration of the effects of EPA and DHA on liver and adipose tissue function and adipokine secretion (Kalupahana N.S., *et al* 2011).

Besides the anti-inflammatory effects and skeletal muscle flexibility improvements, omega-3 fatty acid supplementation also directly prevents excessive adiposity by increasing fatty acid peroxidation in hepatic, adipose and skeletal muscle tissue. It also reduces liponeogenesis in the liver and directly increases adipocyte insulin sensitivity through modulation of adiponectin secretion as illustrated by figure 4 (Kalupahana N.S., *et al* 2011).

Finally, although most of the feline diabetic population has type 2 diabetes, there is a study demonstrating that an increased pancreatic omega-3 fatty acid concentration in transgenic mice protects the beta cells against direct destructive influences like toxins and other diabetes type 1 inducing influences. After supplementation with streptozotocin (this product is toxic towards beta cells) the transgenic mice's beta cell functions were unaffected. Normally streptozotocin supplementation induces severe type 1 diabetes. According to this study these effects were not yet mimicked with an omega-3 fatty acid rich diet, however recommendations towards further research in this field were made. According to this study omega-3 fatty acid supplementation may prove valuable towards the prevention of type 1 diabetes (Bellenger J., *et al* 2011).

Omega-3 fatty acid supplementation as a supportive measure

Although animals do not suffer from cardiovascular complications in the way humans do there is still a host of possible beneficial effects provided by additional omega-3 fatty acid supplementation in diabetic patients.

Omega-3 fatty acid supplementation has been shown to improve blood lipid levels and overall lipid profile, even in diabetic patients (Rudkowska I. 2010). Indeed PUFAS and, more importantly, omega-3 fatty acid supplementation has been shown to even help regulate lipid profile and increase plasma glucose levels during fastening periods. A study has demonstrated that omega-3 fatty acid supplementation will cause an increased activity of the delta-5 desaturase enzyme, thus improving the patient's metabolic profile. This study also demonstrated that although the supplementation of PUFAS will help in improving the metabolic profile of the patient, there is also a strong genetic component responsible for the exact amount of effect the treatment will have (Cormier H.*, et al* 2013).

Omega-3 fatty acid supplementation may also help glucose control in patients suffering from type 2 diabetes. It has even been proven that regular intake of omega 3 fatty acids will slow down the progression of diabetes 2 itself (Rudkowska I. 2010).

A study by Huang T. *et al* (2010) has shown increased intake of omega-3 fatty acids may prove beneficial towards glycemic control. In this study blood markers for insulin resistance and glucose levels were inversely correlated by the amount of omega-3 fatty acids in the diet. Omega-3 fatty acids seem to lessen insulin resistance whilst omega-6 fatty acids have the opposite effect. This suggests a possible role in diet omega-3/6 ratios when dealing with diabetes type 2 according to the authors. The mechanism behind these effects are not yet fully understood but the study suggested membrane fluidity may play a role in the creation of this altered state of insulin sensitivity. It also suggested altered delta-5 desaturase activity could be another possible cause.

As discussed in an earlier chapter increased insulin resistance can also be the result of a pro-inflammatory state. The anti-inflammatory effects of omega-3 fatty acids may prove beneficial in this matter, even at a stage where diabetes 2 itself is already occurring. Studies have shown increased levels of omega-3 fatty acids help reduce the pro-inflammatory state in diabetic patients. This is achieved by lowering the amount of circulating pro-inflammatory signal molecules according to Rudkowska I. (2010).This is also proposed in a review by Guadarrama-López A. *et al* (2014). It concluded that increased omega-3 fatty acid intake will slow progress of inflammatory processes, including type 2 diabetes.

Type 2 diabetes will cause a state of elevated oxidative stress in the patient; however parameters measuring oxidative stress were significantly lowered after low doses of supplemented omega-3 fatty acids. Thus omega-3 fatty acid supplementation will, besides improving the metabolic profile and increasing glycemic control, also lower oxidative stress in the patient under the right circumstances (Jain S., *et al* 2013).

A study by Sarbolouki S.H. *et al* (2010) also recognizes the increased oxidative stress in diabetic patients and the possible role omega-3 fatty acid supplementation could play. This study noted decreased oxidative stress when omega-3 fatty acids were supplemented. It also noted additional vitamin E supplementation was not needed. The exact cause of these results is still unknown.

Type 2 diabetes and insulin resistance result in an abnormal endothelium-dependent vascular dilatation. However a study by Mustada V.A. *et al* (2006) demonstrated vascular motor range seems to normalize back towards the baseline of non-diabetic lean mice when fed an omega-3 rich diet (see figure 5 for reference). This is demonstrated by the figure on the right. The study concluded the feeding of an omega-3 rich diet may prove beneficial for normalizing vascular function in diabetic patients. A possible explanation of this effect could be the altered membrane lipid profile, directly improving vascular function. The indirect enhancement of vascular function due to a decrease in the inflammatory state and/or decrease of the specific lipid profile normally observed in diabetic patients could also be a factor.

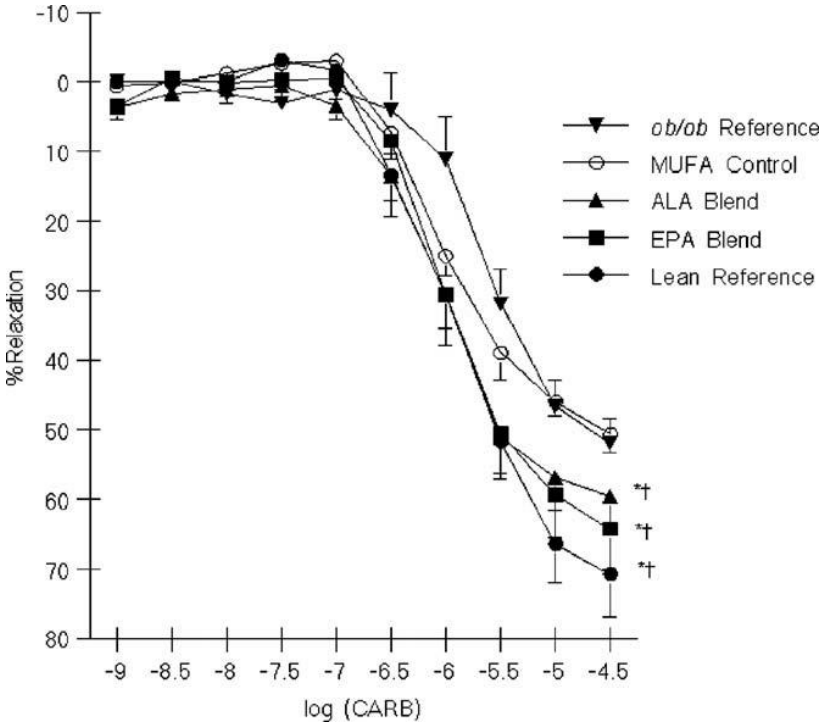

Figure 5. Vascular relaxation parameters in normal mice (lean reference), diabetic obese mice (ob/ob reference) and diabetic mice fed various diets. Mustad V., *et al* (2006)

A common and quite severe complication observed in diabetic patients is the onset of diabetic retinopathy. This condition often results in permanent blindness by ways of retinal damage. However omega-3 fatty acid supplementation has a profound protective effect on the retina. Normally retinal damage in diabetic patients is the result of retinal vascular degeneration, in turn causing the retina to degrade as well. This vascular degeneration is caused by a subtle but constant state of inflammation in

the retinal vascularization. The resulting damage will then be inadequately repaired in diabetic patients. This is caused by a decreased function of endothelial progenitor cells circulating from the bone marrow (EPC). When supplemented with additional omega-3 fatty acids the increased inflammatory state is alleviated by lowering pro-inflammatory signaling. Increased omega-3 fatty acid supplementation will also enhance EPC function, thus increasing repair capabilities of the retinal blood vessels already damaged. The net result is a profound protective effect on the retina in diabetic patients (Tikhonenko M., *et al* 2013).

Although supplementation of omega-3 fatty acids does not significantly lower markers for kidney damage in humans, use of omega-3 fatty acid supplementation in conjunction with renin angiotensin aldosterone system inhibitors (RAAS inhibitors) had remarkable results. Initially the study that found these results was set up to prove or disprove potential beneficial effects of omega-3 fatty acid supplementation. Although there was a progressive decrease of markers for renal injury the results were deemed non-significant. A subgroup containing patients already using RAAS inhibitors did see significant reductions in nearly all markers indicating renal injury. This demonstrates the potential beneficial effects of using omega-3 fatty acid supplements in conjunction with RAAS inhibitors when dealing with (diabetic) chronic kidney disease. However according to the authors further studies were needed (Miller E.R. *et al* 2013).

Another common complication associated with type 2 diabetes is non-alcoholic fatty liver disease. This disease is also associated with metabolic syndrome and obesity (Cusi K. 2009). A study by Petit J.M. *et al* (2012) demonstrated a decrease in steatosis in diabetic patients when administered additional chain poly-unsaturated fatty acids, thus concluding dietary supplementation may prove beneficial for diabetic patients.

Type 2 diabetes is associated in humans with an increased blood pressure. Supplementation of omega-3 fatty acids has been shown to lower diastolic blood pressure. Fibrinogen, heartrate and systolic blood pressure were also affected. A slight decrease in these parameters was noted, however the results were statistically insignificant according to Hartweg, *et al* (2007) and required further studying to be more conclusive.

Besides causing problems in the peripheral nervous systems, diabetes also impairs neuron function in the central nervous system by decreasing neuron excitability, resulting in impaired cognitive functions and memory functions. Interestingly enough increased intake of omega-3 fatty acids seems to improve neuron excitability in the brains of diabetic rats, dampening these adverse effects to a degree. However, the exact mechanism behind this positive influence needs further research and is yet to be fully understood (Yang R.H. *et al* 2012).

Possible risks associated with a high poly unsaturated fatty acid intake

Although there are several benefits observed feeding diets containing a high dose of poly unsaturated fatty acids (PUFAS) there are also some harmful effects associated with such a diets.

Diets containing high levels of PUFAS through fish oil supplementation have been demonstrated to be harmful for the liver by raising liver fat content. This is much in the same way a diet with elevated saturated fatty acid content will do. Such a diet also induced elevated oxidative stress in liver and muscle tissue (Feillet-Coudray C., *et al* 2013).

Because increasing the intake of unsaturated fatty acids results in increased oxidative stress there will also be an elevated need for anti-oxidants such as vitamin E. One study for example noted an increase in unsaturated fatty acid intake raised the required vitamin E intake (Howitt M.K. 1960). Another study has shown that most supplements rich in poly unsaturated fatty acids have a low vitamin E to PUFA ratio, meaning those supplements would deplete vitamin E reserves (Harris P.L. and Embree N.D. 1963).

Care should be taken to use the right ratio of omega-3 and omega-6 fatty acids supplemented. Too high of an omega-6 fatty acid intake may have adverse effects. It could result in an elevated risk of developing insulin resistance and the promotion of hyperinsulinemia (Yam D., *et al* 1996). High omega-6/omega-3 ratios are also associated with a shift from an anti-inflammatory profile towards a pro-inflammatory profile. This will promote the onset of chronic inflammatory diseases like inflammatory bowel disease, rheumatoid arthritis and non-alcoholic fatty liver disease. A good balance between omega-6 and omega-3 fatty acids is thus recommended according to Patterson E., *et al* (2012).

Feeding animals high doses of omega-3 fatty acids may also result in gastrointestinal complications. In a study using dietary fish oil supplements diarrhea and vomiting were reported in some animals (Fritsch D., *et al* 2010). However, abnormal stool quality can be minimized by gradually increasing the diet fat content over time as opposed to directly starting with the full dose (Roudebush P., *et al* 2004).

A study performed by Guillot N. *et al* (2009) reported reduced platelet function after supplementing humans with additional omega-3 fatty acids in their diet. This change in platelet function already occurs when supplements were given in low doses. This relationship between supplementation and altered function was of a non-linear nature and according to the study no inhibition of whole thrombocyte aggregation would occur.

Finally it would be beneficial to take the supplemented fatty acid's energetic value in account when providing the new diet to prevent unwanted weight gain (Lenox C.E. and Bauer J.E. 2013).

Discussion

In light of the advantages and disadvantages described in this article one could easily understand omega-3 fatty acid supplementation being seen as a very attractive therapy or extra measure in the treatment of either obesity or diabetes 2. Supplementation has various benefits that will help the animal in coping with his/her condition whilst at the same time proving beneficial in situations where prevention is more important.

Although there are some possible risks involved, those risks are arguably fairly minor, especially when vitamin E supplements are provided. However, this doesn't mean omega-3 supplementation is entirely risk free, thus overuse should be avoided whenever possible.

It has to be noted, however, that most of the studies found discussing the topics of this article mostly focused on possible treatments in human patients. Fortunately cats and humans are comparable enough that one could argue the differences involved being almost non-existent when it comes to supplementation of omega-3 fatty acids. Still, more studies aimed towards use in animals (and specifically cats and dogs) are recommended.

Most studies found were fairly recent (most were published close to 2013), suggesting the application of omega-3 fatty acids as possible treatment in diabetic patients (or patients at risk) is still a fairly new field of study.

A lot of the articles found noted that quite a few of the possible effects observed were not deemed significant due to low power of the studies involved. A lot of articles also noted that few of the mechanisms behind observed effects are fully understood. Generally further research in this field of study is therefore, again, recommended.

In summary: in light of recent results, omega-3 supplementation is certainly recommended for the motivated owner if care is taken to prevent negative side effects. Supplementation could very well be a great way to improve quality of life for the patient and enhance results of regular treatment for obesity and/or diabetes 2. However, because a lot is still unknown further studies are still fully recommended to provide more conclusive and/or reliable information for vet and owner alike.

Sources

- Appleton D.J., Rand J.S. and Sunvold G.D. (2001). Insulin sensitivity decreases with obesity, and lean cats with low insulin sensitivity are at greatest risk of glucose intolerance with weight gain. Journal of Feline Medicine and Surgery 3, 211–228
- Bellenger J., Bellenger S., Bataille A., Massey K.A., Nicolaou A., Rialland M., Tessier C., Kang J.X. and Narce M. (2011). High pancreatic n-3 fatty acids prevent STZ-induced diabetes in fat-1 mice: inflammatory pathway inhibition. Diabetes 60, 1090-1099
- Cormier H., Rudkowska I., Thifault E., Lemieux S., Couture P. and Vohl M. (2013). Polymorphisms in fatty acid desaturase (fads) gene cluster: effects on glycemic controls following an omega-3 polyunsaturated fatty acids (pufa) supplementation. Genes 4, 485-498
- Cusi K. (2009). Nonalcoholic fatty liver disease in type 2 diabetes mellitus. Current Opinion in Endocrinology, Diabetes and Obesity 16, 141-149
- Feillet-Coudray C., Aoun M., Fouret G., Bonafos B., Ramos J., Casas F., Cristol J.P. and Coudray C. (2013). Effects of long-term administration of saturated and n-3 fatty acid-rich diets on lipid utilisation and oxidative stress in rat liver and muscle tissues. British Journal of Nutrition 110, 1789–1802
- Flock M.R., J. Rogers C.J., Prabhu K.S. and Kris-Etherton P.M. (2013). Immunometabolic role of long-chain omega-3 fatty acids in obesity-induced inflammation. Diabetes/metabolism research and reviews 29, 431–445
- Fritsch D., Allen T.A., Dodd C.E., Jewell D.E, Sixby K.A., Leventhal P.S. and Hahn K.A. (2010). Dose-titration effects of fish oil in osteoarthritic dogs. Journal of veterinary Internal medicine 24, 1020–1026
- Guadarrama-López A.L., Valdés-Ramos R., and Martínez-Carrillo B.E. (2014) Type 2 diabetes, PUFAS, and vitamin D: their relation to inflammation. Journal of Immunology Research
- Guillot N., Caillet E., Laville M., Calzada C., Lagarde M. and Ve´ricel E. (2009). Increasing intakes of the long-chain omega-3 docosahexaenoic acid: effects on platelet functions and redox status in healthy men. The FASEB Journal 23, 2909-2916
- Harris P.L. and Embree N.D. (1963). Quantitative consideration of the effect of polyunsaturated fatty acid content of the diet upon the requirements for vitamin E. American Journal of Clinical Nutrition 13, 385-392
- Hartweg J., Farmer A.J., Holman R.R. and Neil H.A.W. (2007). Meta-analysis of the effects of n-3 polyunsaturated fatty acids on haematological and thrombogenic factors in type 2 diabetes. Diabetologia 50, 250–258
- Henson M.S. and O'Brien T.D. (2006). Feline Models of Type 2 Diabetes Mellitus. Institute for Laboratory Animal Research journal 47, 181-185

- Hoenig M., Thomaseth K., Waldron M. and Ferguson D.C. (2007). Insulin sensitivity, fat distribution and adipocytokine response to different diets in lean and obese cats before and after weight loss. American journal of physiology. Regulatory, Integrative and Comparative Physiology 292, 227–234
- Hoenig M. (2012). The cat as a model for human obesity and diabetes. Journal of Diabetes Science and Technology 6, 525-533
- Horakova O., Medrikova D., van Schothorst E.M, Bunschoten A., Flachs P., Kus V., Kuda O., Bardova K., Janovska P., Hensler M., Rossmeisl M., Wang-Sattler R., Prehn C., Adamski J., Illig T., Keijer J. and Kopecky J. (2012). Preservation of Metabolic Flexibility in Skeletal Muscle by a Combined Use of n-3 PUFA and Rosiglitazone in Dietary Obese Mice. PLOS one 7
- Howitt M.K. (1960). Vitamin E and lipid metabolism in man American Journal of clinical Nutrition 451, 451–461
- Huang T., Wahlqvist M.L, Xu T., Xu A., Zhang A. and Li D. (2010). Increased plasma n-3 polyunsaturated fatty acidis associated with improved insulin sensitivity in type 2 diabetes in China. Molecular Nutrition and Food Research 54, 112–119
- Jain S., Gaiha M., Bhattacharjee J. and Anuradha S. (2002). Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress - a prospective preliminary study. Journal of the Association of Physicians of India 50, 1028-33
- Kalupahana N.S., Claycombe K.J. and Moustaid-Moussa N. (2011). N-3 Fatty Acids Alleviate Adipose Tissue inflammation and Insulin Resistance: mechanistic Insights. Advances in Nutrition 2, 304–316
- Kelley D.E., Mandarino L.J. (2000). Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes 49, 677-683
- Kim J., Li Y. AND Watkins B.A.: Fat to treat fat: Emerging relationship between dietary PUFA, endocannabinoids, and obesity. Prostaglandins & other Lipid Mediators 32–41 (2013), p.104–105
- Kris-Etherton P.M., Harris W.S. and Appel L.J. (2002). Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. Circulation 106, 2747-2757
- Lamping K.L., Nuno D.W., Coppey L.J., Holmes A.J., Hu S., Oltman C.L., Norris A.W. and Yorek M.A.: Modification of high saturated fat diet with n-3 polyunsaturated fat improves glucose intolerance and vascular dysfunction. Diabetes, obesity and metabolism 15:2 (2013), p.144–152
- Lenox C.E. and Bauer J.E. (2013). Adverse effects of omega-3 fatty acids in dogs and cats. Journal of veterinary internal medicine 2, 217-226
- Liu H., Qiua Y., Mub Y., Zhangc X., Liu L., Houa X., Zhanga L., Xua X., Ji A., Caoa R., Yanga R. and Wanga F. (2013). A high ratio of dietary n-3/n-6 polyunsaturated fatty acids improves obesity-linked inflammation and insulin resistance through suppressing activation of TLR4 in SD rats. Nutrition research 33, 849– 858

- McCann T.M., Simpson K.E., Shaw D.J., Butt J.A. and Gunn-Moore D.A. (2007). Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. Journal of Feline Medicine and Surgery 9, 289–299
- Miller E.R, Juraschek S.P., Anderson C.A., Guallar E., Henoch-Ryugo K., Charleston J., Turban S., Bennett M.R. and Appel L.J. (2013). The Effects of n-3 Long-Chain Polyunsaturated Fatty Acid Supplementation on Biomarkers of Kidney Injury in Adults with Diabetes. Diabetes Care 36, 1462–1469.
- Mori T.A. and Beilin L.J. (2004). Omega-3 Fatty Acids and Inflammation. Current Atherosclerosis Reports 6, 461–467
- Mustada V.A., DeMichelea S., Huanga Y., Mikab A., Lubbersb N., Berthiaumeb N., Polakowskib J. and Zinkerb B. (2006). Differential effects of n-3 polyunsaturated fatty acids on metabolic control and vascular reactivity in the type 2 diabetic ob/ob mouse. Metabolism Clinical and Experimental 55, 1365–1374
- Nelson D. and Cox M.M. (2008): Lehninger - Principles of biochemistry, fifth edition, W.H. Freeman and Company, 345
- Nelson R.W. and Reusch C.E. (2014). Classification and etiology of diabetes in dogs and cats. Journal of endocrinology 222, 1-9
- Nettleton J.A. (1991). Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. Journal of the American Dietetic Association 91, 331-337
- Patterson E., Wall R., Fitzgerald G.F., Ross R.P. and Stanton C. (2012). Health implications of high dietary omega-6 polyunsaturated fatty acids. Journal of Nutrition and Metabolism 2012
- Pawlosky R., Barnes A. and Salem N. (1994). Essential fatty acid metabolism in the feline: relationship between liver and brain production of long-chain polyunsaturated fatty acids. Journal of Lipid Research 35, 2032-2040
- Petit J.M., Guiu B., Duvillard L., Jooste V., Brindisi M.C. Athias A., Bouillet B., Habchi M., Cottet V.,Gambert P., Hillon P., Cercueil J.P. and B. Verges B. (2012). Increased erythrocytes n-3 and n-6 polyunsaturated fatty acids is significantly associated with a lower prevalence of steatosis in patients with type 2 diabetes. Clinical Nutrition 31, 520-525
- Rivers J.P., Sinclair A.J. and Crawford M.A (1975). Inability of the cat to desaturate essential fatty acids. Nature 258, 171-173
- Robinson L.E. and Mazurak V.C. (2013). N-3 Polyunsaturated Fatty Acids: Relationship to Inflammation in Healthy Adults and Adults Exhibiting Features of Metabolic Syndrome. Lipids 48, 319–332
- Roudebush P., Davenport D.J. and Novotny B.J. (2004). The use of nutraceuticals in cancer therapy. The veterinary clinics small animal practice 34, 249–269
- Rudkowska I. (2010). Fish oils for cardiovascular disease: Impact on diabetes. Maturitas 67, 25–28

- Sallander M., Eliasson J. and Hedhammar Å. (2012). Prevalence and risk factors for the development of diabetes mellitus in Swedish cats. Acta veterinaria scandinavica 54
- Sarbolouki S.H., Djalali M., Dorosty A.R., Djazayery S.A., Eshraghian M.R., Ebadi S.A.R. and Hashemi S.B. (2010). Effects of EPA and vitamin e on serum enzymatic antioxidants and peroxidation indices in patients with type ii diabetes mellitus. Iranian Journal of Public Health 9, 82-91
- Scarlett J.M. and Donoghue S. (1998). Associations between body condition and disease in cats. Journal of the American veterinary medical association 212, 1725–1731
- Scott-Moncrieff J.C. (2010). Insulin Resistance in Cats. The Veterinary clinics of North America small animal practice volume 40, 241-257
- Smith J.R., Vrono Z., Rapoport G.S., Turek M.M. and Creevy K.E. (2012). A survey of southeastern United States veterinarians' preferences for managing cats with diabetes mellitus. Journal of feline medicine and surgery 14, 716-722
- Spencer M., Finlin B.S., Unal R., Zhu B., Morris A.J., Shipp L.R., Lee J., Walton R.G., Adu A., Erfani R., Campbell M., McGehee R.E., Peterson C.A. and Kern P.A. (2013). Omega-3 Fatty Acids Reduce Adipose Tissue Macrophages in Human Subjects With Insulin Resistance. Diabetes 62, 1709–1717
- Tikhonenko M., Lydic T.A., Opreanu M., Calzi S.L., Bozack S., McSorley K.M., Sochacki A.L., Faber M.S, Hazra S., Duclos S., Guberski D., Reid G.E., Grant M.B and Busik J.V (2013). N-3 Polyunsaturated fatty acids prevent diabetic retinopathy by inhibition of retinal vascular damage and enhanced endothelial progenitor cell reparative function. PLOS one 8
- Wikipedia. Omega-3 fatty acid. http://en.wikipedia.org/wiki/Omega-3_fatty_acid (consulted at 30/03/2015)
- Yam D., Eliraz A. and Berry E.M. (1996). Diet and disease - the Israeli paradox: possible dangers of a high omega-6 polyunsaturated fatty acid diet. Israeli journal of medical science 32, 1134-1143
- Yang R.H., Wang F., Hou X.H., Cao Z.P., Wang B., Xu X.N. and Hu S.J. (2012). Dietary omega-3 polyunsaturated fatty acids improves learning performance of diabetic rats by regulating the neuron excitability. Neuroscience 212, 93–103