

Pilot study: serum concentration of insulin-like growth factor 1 in intact and spayed dogs

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Abstract

Insulin-like growth factor 1 (IGF-1) has been positively associated with body size and negatively associated with lifespan in dogs. Gonadectomy has been associated with increased lifespan in dogs. Insulin-like growth factor 1 was assayed in serum harvested from 50 intact and 50 spayed female dogs as they were surrendered to a humane organization. Serum IGF-1 concentrations were significantly lower in spayed female dogs than in intact bitches. Overlap in serum IGF-1 concentrations in the groups in this study was too great to permit a single sample to be used to differentiate spayed from intact dogs.

Keywords: Insulin-like growth factor 1, gonadectomy, ovariectomy, ovariohysterectomy, lifespan

Introduction

Insulin-like growth factor 1 is a protein similar in appearance to pro-insulin at the molecular level that binds to insulin receptors with low affinity.¹ The insulin/IGF-1 signaling pathway mediates growth by stimulating increase in cell size and number through the action of insulin-like peptides.² The growth hormone (GH)/IGF-1 signaling pathway also stimulates growth. Growth hormone stimulates release of IGF-1 which in turn stimulates anabolic and mitogenic activity of GH.^{1,3} Insulin-like growth factor 1 receptors are present in almost all tissues in humans during embryogenesis and IGF-1 has been demonstrated as an essential component of embryogenesis of the gonads in mice.⁴ In adult humans, IGF-1 is produced primarily in the liver but also is produced in other tissues and may act synergistically with GH at distant sites or locally.¹

Variation in concentration of IGF-1 has been associated with physical characteristics of dogs and with various disorders (Table).⁵⁻²² A positive correlation of IGF-1 concentrations with height, weight, and general body size of dogs has been reported.^{5,10,23} Genetic studies have identified IGF-1 as a primary determinant of variant body size within dog breeds.²⁴⁻²⁶

Many studies have documented increased lifespan as a benefit of gonadectomy.^{6,18-22} Exact mechanism of this association has not been defined although some authors cite as possible reasons increased owner investment in animals they have paid to have altered and decrease in risky behaviors by the dogs after gonadectomy, such as roaming.¹⁸⁻²⁰ Cause of death varies between populations of intact and gonadectomized dogs, with intact dogs more likely to die of infectious disease or trauma and gonadectomized dogs more likely to die of cancer.²² Decreased concentrations of IGF-1 have been associated with increased longevity in many species.^{15,16,27-32} A negative correlation of concentrations of IGF-1 with age has been reported in dogs.⁵ When comparing small breed to large breed dogs, the increased lifespan of smaller dogs appears to be due to slower aging in those breeds.³³ It has been suggested that lower concentrations of IGF-1 may delay aging and extend lifespan, perhaps through association with greater resistance to oxidative stress.^{32,34-36}

Data from one study suggested that baseline concentrations of IGF-1 were lower in gonadectomized dogs than in intact dogs.⁵ This suggests that IGF-1 may be associated with the increased longevity noted after gonadectomy. If decreased concentrations of IGF-1 can be demonstrated in ovariectomized versus intact bitches, it would lend support to the hypothesis that decrease in IGF-1 is the cause for this effect.

If values are well enough differentiated between intact and ovariectomized dogs, this could be another tool to help humane organizations and practicing veterinarians determine intact status in female dogs. While non-invasive tests for luteinizing hormone (LH) and anti-Mullerian hormone (AMH) to determine intact status have been described, many people rely on palpation of a spay scar, which is not a specific measure of intact status, or waiting for the dog to show signs of heat, which increases risk of unintentional breeding and hormone exposure associated with mammary neoplasia and pyometra.^{37,38}

Skilled practitioners with access to high quality equipment also may be able to identify whether or not a dog is intact using ultrasonography; negative findings may be equivocal.

Hypotheses evaluated in this study were the following:

Hypothesis #1: Serum IGF-1 concentrations will be significantly lower in spayed female dogs than in intact bitches.

Hypothesis #2: The difference in concentration between spayed and intact dogs will be great enough to permit measurement of IGF-1 concentration in serum to be used as a sensitive and specific measure of intact status in female dogs.

Materials and methods

Blood was drawn from 50 spayed and 50 intact female dogs as they entered a humane organization.* Animals were relinquished by appointment or were transferred from another humane facility. Animals were enrolled as they were relinquished or transferred; no specific exclusion criteria were required. Breed and age of dog were identified by the owner of relinquished animals; for all other dogs, breed and age were estimated by trained intake staff. Bitches were identified as spayed by a spay scar (24 dogs) or a tattoo (26 dogs). Duration from spay to relinquishment was not recorded. Bitches admitted as intact underwent ovariohysterectomy within days of entry, before being placed for adoption. Blood was collected at the time of admission, spun down, and the serum removed. Serum was frozen and shipped as directed by the commercial laboratory which performed assay for IGF-1.^{†b}

Statistical analysis included descriptive statistics, Pearson's correlation coefficient, and the unpaired t-test. Significance was set at $p < 0.05$.

Results

Breeds of dogs in the intact group were American Blue Heeler cross (1), Australian Cattle Dog cross (1), Basset hound cross (2), Beagle (1), Beagle cross (1), Boxer (1), Catahoula Leopard dog cross (1), Chihuahua (12), Collie cross (1), Dachshund cross (1), German Shepherd (1), German shepherd cross (4), Golden retriever cross (1), Hound cross (5), Jack Russell terrier cross (1), Labrador retriever cross (5), Miniature pinscher cross (1), Pit bull (1), Pit bull cross (1), Retriever cross (1), Shih tzu (2), and Terrier cross (5). Breeds of dogs in the spayed group were American Staffordshire Terrier (1), Australian cattle dog (1), Beagle cross (1), Basenji cross (1), Border terrier cross (1), Chihuahua (27), Chow chow cross (1), Coonhound cross (1) Hound cross (2), Labrador retriever (1), Labrador retriever cross (1), Manchester terrier (1), Retriever cross (3), Rottweiler (1), St Bernard (1), Shepherd cross (3), Shih tzu cross (1), and Terrier cross (2).

Overall mean weight was 26.3 ± 18.5 lbs. Mean weight of the intact dogs was 28.1 ± 16.7 lbs. Mean weight of the spayed dogs was 24.5 ± 20.0 lbs. Difference in weight between the groups was not significant.

Overall mean age was 19.2 ± 9.3 months. Age was not correlated with IGF-1 concentration ($R = -0.17$). Mean age of the intact dogs was 21.9 ± 9.7 months. Mean age of the spayed dogs was 16.5 ± 8.1 months. Difference in age between the groups was significant ($p = 0.003$).

Overall mean IGF-1 concentration was 37.3 ± 25.0 nmol/L. Overall correlation between weight and IGF-1 concentration was moderately positive ($R = 0.67$). Mean IGF-1 concentration in intact dogs was 42.1 ± 27.6 nmol/L and was positively correlated with weight ($R = 0.62$). Mean IGF-1 concentration in spayed dogs was 32.5 ± 21.3 nmol/L and was strongly correlated with weight ($R = 0.74$). Difference in IGF-1 concentration between the groups was significant ($p = 0.05$).

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Discussion

The primary concern about this study is the lack of information about the dogs due to sampling from a humane society population. It is clear that all dogs were correctly identified as intact, as they were spayed within days of entering the facility. However, it is possible that some dogs identified as having been spayed were actually intact, and did not show signs of heat while in the facility prior to adoption. However, this would have artificially skewed the mean concentration for IGF-1 in the population of gonadectomized dogs higher than was reported, which simply strengthens the findings of the study. We also do not know if dogs identified as spayed had undergone ovariectomy or ovariohysterectomy. It is possible, although very unlikely in the region from which this sample was drawn, that some dogs identified as spayed had undergone hysterectomy. Inability to define exact means of surgical sterilization in all dogs unavoidably introduced variation.

No information was gathered about body condition score of dogs from which samples were drawn. Obesity is common in gonadectomized dogs.³⁹⁻⁴⁴ Obesity is associated with increased concentrations of IGF-1 in humans.¹¹⁻¹³ If the same is true in dogs and if the gonadectomized dogs in this study were more obese than the intact dogs in the study, again this would have skewed the true concentration of IGF-1 higher in the gonadectomized dogs, strengthening the findings of the study. Future studies would benefit from normalization of IGF-1 concentrations with body condition scoring.

This study does not address the actual mechanisms by which either gonadectomy or decrease in concentrations of IGF-1 increase lifespan. The majority of studies to date have demonstrated that gonadectomy increases lifespan but in one population of exceptionally long-lived Rottweilers, remaining intact (ovarian exposure) was associated with increased lifespan, suggesting that some factor released from the ovary promoted longevity in that group of dogs.⁴⁵ This increase in lifespan was not associated with intensity or tempo of reproductive effort.⁴⁶ Canine ovarian follicles contain IGF-1 but concentrations are well correlated with plasma concentrations of IGF-1, suggesting a lack of direct connection between presence or absence of ovaries and secretion of IGF-1.²³ Because duration from spaying to relinquishment was not recorded and may well not have been known for many of the dogs, it is possible that the variation noted in this study was altered by variability in time from gonadectomy to a rise in IGF-1 concentrations in serum.

Similarly, stage of the estrous cycle was not identified in those bitches who underwent ovariohysterectomy at the humane society. It has been demonstrated that concentrations of GH and other growth factors, including IGF-1, are higher during the luteal phase of the estrous cycle in bitches.⁴⁷⁻⁴⁹ Considerations of cost and logistics of the surgery service at the humane organization supporting this study prevented use of serum progesterone concentration measurement or histopathologic assessment of excised ovaries as a means of determining stage of the estrous cycle of bitches in the intact group.

Hypothesis #1 was supported in this study as spayed dogs had significantly lower serum concentrations of IGF-1 than intact dogs in this sample. Although there was a positive correlation of weight with IGF-1 concentration, there was no significant difference in weight between the groups, removing that variable as a cause for the difference in this sample. There was no correlation of age with IGF-1 concentration, so although there was a significant difference in age between the groups, this variable cannot be a cause for the difference in this sample.

Hypothesis #2 was not supported in this study. Overlap in serum IGF-1 concentrations in the groups in this study was too great to permit a single sample to be used to differentiate spayed from intact dogs.

Conclusion

There is a growing body of evidence documenting benefits and detriments of gonadectomy in dogs.⁵⁰⁻⁵⁴ In general, benefits of gonadectomy of female dogs are a reduction in incidence of mammary neoplasia and pyometra when aged. Reported detriments associated with gonadectomy include neoplasia, including osteosarcoma, hemangiosarcoma, transitional cell carcinoma, lymphosarcoma, and mast cell tumor; orthopedic disease, including anterior cruciate ligament injury and hip dysplasia; obesity; and urinary incontinence. Better understanding of the mechanisms underlying physiologic changes induced

by gonadectomy, including effects of a decrease in concentrations of IGF-1 and other hormones, will permit veterinarians to make the best decisions regarding recommendations for gonadectomy of individuals or populations of dogs to balance pet overpopulation with individual animal health.

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Table. Causes of variation in blood concentrations of IGF-1 and in lifespan of dogs

ASSOCIATED WITH DECREASED IGF-1	ASSOCIATED WITH INCREASED IGF-1
<ul style="list-style-type: none"> - Gonadectomy - Increasing age - Small body size - Acute inflammation including post-surgical inflammation, disease conditions - Chronic inflammation 	<ul style="list-style-type: none"> - Large body size - Chronic disorders including obesity
ASSOCIATED WITH DECREASED LIFESPAN	ASSOCIATED WITH INCREASED LIFESPAN
<ul style="list-style-type: none"> - Large body size - Obesity 	<ul style="list-style-type: none"> - Gonadectomy

