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# Big Brains and Blood Glucose: Common Ground for Diabetes Mellitus in Humans and Healthy Dolphins

**Stephanie K Venn-Watson[1,*] and Sam H Ridgway[1,2]**

**Healthy Atlantic bottlenose dolphins (*Tursiops truncatus*) have a sustained postprandial hyperglycemia, producing a prolonged glucose tolerance curve and a transient, diabetes mellitus-like state during 6 to 72 h of fasting. To further assess dolphins as comparative models for diabetes in humans, we hypothesized that a suite of hematological and clinical biochemistry changes during the fasting state may mimic those reported in humans with diabetes. We conducted a retrospective analysis of covariance to compare fasting and nonfasting hematologic and serum biochemical data, including 1161 routine blood samples from 52 healthy bottlenose dolphins (age, 1 to 49 y; male and female) collected during 1998 through 2005. Most changes found in dolphins during the fasting state—including significantly increased glucose, platelets, gamma-glutamyl transpeptidase, and alkaline phosphatase; significantly decreased serum uric acid; and shifts toward a metabolic acidodic state (significantly increased blood $CO_2$)—have been previously associated with diabetes mellitus in humans. Therefore, healthy bottlenose dolphins may be the first complete and natural comparative animal model for diabetes mellitus in humans. Similarities between dolphins and humans, including metabolic changes associated with high-protein, low-carbohydrate diets; large brain-to-mass ratios; high central nervous system demands for glucose; and similarly unique blood glucose-carrying capacities should be further assessed to better understand the potential evolutionary paths of diabetes mellitus in these 2 species.**

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; MMP, US Navy Marine Mammal Program

Atlantic bottlenose dolphins (*Tursiops truncatus*) have a prolonged glucose tolerance curve and naturally maintain a fasting hyperglycemia, similar to diabetes mellitus in humans.[35,38] In addition to fasting hyperglycemia, people with diabetes mellitus may have abnormalities in hematologic and serum biochemical variables, including increased platelet counts,[10,40] alkaline phosphatase,[26] and gamma-glutamyl transpeptidase (GGT);[3,24] decreased serum uric acid;[14,29] and acid–base imbalances due to ketoacidosis.[4] Although the direct cause of acid–base imbalances has been explained for humans with diabetes,[20] the reasons for other blood changes, including hypouricemia, thrombocytosis, and increased GGT, are still being researched.

For more than 40 y, the US Navy Marine Mammal Program (MMP) has housed a population of bottlenose dolphins that eat naturally high-protein diets, live in the open ocean, and are provided high-quality medical and preventive care throughout their lifetime. New additions to the dolphin population since the 1980s have been captive-bred or received from other marine mammal facilities. Standardized health data and voluntary blood samples are collected routinely, uniquely enabling the MMP to amass large medical databases on healthy dolphins in their natural environment at all age stages. As such, data from the MMP may be used to conduct comparative studies between marine and terrestrial animals.

The discovery of new comparative animal models for diabetes mellitus may provide valuable evolutionary insight for diabetes in humans. Although animal models including rats, mice, dogs, pigs, and cats have been used to study diabetes, a single species has not been identified that fully complements type 2 diabetes mellitus in humans.[8,22] To test a hypothesized parallel between fasting dolphins and humans with diabetes, we conducted a retrospective study by using animal health data from the MMP to compare hematologic and serum biochemical values in healthy bottlenose dolphins that had recently been fed with those of healthy bottlenose dolphins fasted overnight (typically 10 to 14 h). Significant differences found in the fasted dolphin population subsequently were compared with blood changes reported for humans with diabetes.

## Materials and Methods

The MMP is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International and adheres to the national standards of the US Public Health Service Policy on the Humane Care and Use of Laboratory Animals and the Animal Welfare Act. As required by the Department of Defense, the MMP's animal care and use program is routinely reviewed by an institutional animal care and use committee and the Department of Defense Bureau of Medicine.

**Sample collection, storage, and analysis.** Blood samples were collected from the central tail vein (periarterial venous retia) from animals trained to present their tails voluntarily for sampling or by using behavioral conditioning out of the water on a foam mat during a routine physical exam. Sample volumes typically ranged from 10 to 30 ml and were collected using 20- or 21-gauge, 1.5-in.

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*[1]US Navy Marine Mammal Program, San Diego, CA; [2]Department of Pathology, School of Medicine, University of California San Diego, La Jolla, CA.*
*[*]Corresponding author. Email: stephanie.wong@navy.mil*

**Table 1.** Comparisons of study sample population with a current Atlantic bottlenose dolphin (*Tursiops truncatus*) population at the Navy Marine Mammal Program

| | Study samples (17 Aug 98–31 Dec 06; n = 1161) | | Study population (Dec 2005; n = 52) | | Total population (Dec 2006; n = 67) | |
|---|---|---|---|---|---|---|
| Descriptor | n | % | n | % | n | % |
| Gender | | | | | | |
| Female | 535 | 46.1 | 23 | 44.2 | 31 | 46.3 |
| Male | 626 | 53.9 | 29 | 55.8 | 36 | 53.7 |
| Age categories | | | | | | |
| 1–5 y | 103 | 8.9 | 6 | 11.5 | 9 | 13.4 |
| >5–10 y | 81 | 7.0 | 6 | 11.5 | 7 | 10.5 |
| >10–30 y | 707 | 60.9 | 31 | 59.6 | 38 | 56.7 |
| >30 y | 270 | 23.3 | 9 | 17.3 | 13 | 19.4 |
| Median age (y) | 21.8 (range, 1.3–48.5) | | 25.0 (range, 3.5–49.0) | | 24.0 (range, 1.0–49.0) | |

vacuum phlebotomy needles (Vacutainer Systems, Becton Dickinson, Rutherford, NJ). Blood was collected into serum separator and ethylenediaminetetraacetic acid tubes for serum chemistries and complete blood counts, respectively. Samples marked as 'fasting' typically were collected 12 to 14 h after an animal's most recent feeding.

Samples were chilled for 30 min and centrifuged within 2 h. Centrifugation was performed at 1006 × *g* at 21 °C for 10 min. Fibrin clots were removed, and serum was transferred to a 5-ml plastic tube for transport. Whole blood was submitted for analysis in ethylenediaminetetraacetic acid vacuum phlebotomy tubes. All samples were sent on ice via courier to a commercial diagnostic laboratory (Quest Diagnostic Laboratories, San Diego, CA) for analysis. Automated analyzers were used for hematology (Coulter LH 750, Beckman Coulter, Fullerton, CA) and serum chemistry analysis (model AU600, Olympus America, Center Valley, PA). The diagnostic laboratory routinely calibrated diagnostic equipment before use, maintained a quality control program, and had more than 20 y experience in analysis of dolphin blood samples.

The following hematologic and serum chemistry variables were measured and incorporated into the study: total white blood cell count, hematocrit, platelets, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, glucose, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, carbon dioxide, total protein, albumin, globulins, cholesterol, triglyceride, calcium, inorganic phosphorus, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), iron, creatinine phosphokinase (CPK), and erythrocyte sedimentation rate (ESR). Hematologic and serum biochemical values were entered into a central electronic database and linked to animal information, including species, location, gender, birth date, fasting status, and medications.

**Definitions and exclusion criteria.** Study data were limited to 'healthy' samples, defined as routine, nonhemolyzed blood samples collected from Atlantic bottlenose dolphins in our population that had no known chronic or acute disease at the time of collection; no follow-up clinical blood sample collected within 14 d after the routine sample date; and no treatment with antimicrobials at the time of collection. 'Routine' was defined as a sample collected during a scheduled physical examination or practice blood draw that was not for the purpose of a clinical work-up; blood samples were categorized as routine by attending veterinarians at the time of the blood collection. Blood values included in the study were limited to those reported by the single commercial laboratory indicated; due to the potential for interlaboratory variation, blood results reported by other sources were excluded.

**Statistics.** In addition to hematologic and serum biochemical data, the following variables were included in the analysis: animal identification number, genus, species, gender, age (that is, blood collection date minus birth date), status of sample (hemolyzed or normal), fasting status, and reason for sample collection (routine, initial, or follow-up).

Data were analyzed by using statistics software (SAS release 8e, SAS Institute, Cary, NC). Previously conducted inhouse analyses determined that age and sex significantly affected many blood variable values (data not shown), necessitating control of these confounding factors. Therefore, mean blood values were compared according to fasting status, controlling for gender and age, by analysis of covariance. A general linear model (PROC GLM; CLASS gender fasting; MODEL [blood variables a, b, c…] = age gender fasting; LSMEANS fasting) was applied to control for differences in numbers of samples submitted per animal. Because the nature of large datasets, a type I SS *P* value of less than 0.01 (instead of 0.05) was defined as statistically significant. Mean comparisons were reported by using least-squares means that controlled for potential variance due to age and gender.

## Results

A total of 1161 samples were collected from 52 animals that were healthy at the time of the blood draw. The distribution of study samples and animals by gender and age were comparable with the current MMP dolphin population (Table 1).

Of blood samples included in the study, 639 (55%) were collected from dolphins fasted overnight for 10 to 14 h, and 522 (45%) samples were collected from dolphins that had been fed within 6 h. Of 30 hematologic and serum biochemical variables analyzed, 13 (43.3%) had significant ($P < 0.01$) differences by fasting status, after effects of age and gender were controlled (Tables 2 and 3). The following hematologic and serum biochemical variables had significantly ($P < 0.01$) lower values in fasted samples compared with nonfasted samples: blood urea nitrogen, potassium, carbon dioxide, triglycerides, and uric acid. Platelet levels, chloride, glucose, creatinine, alkaline phosphatase, GGT, and CPK were significantly higher in fasted compared with nonfasted samples.

Fasting status did not alter total white blood cell count, hematocrit, absolute neutrophil count, absolute lymphocyte count,

**Table 2.** Comparisons (least squares means) of hematologic values of healthy *Tursiops truncatus* by fasting status, controlled for age group, gender, and number of samples submitted, Aug 1998–Dec 2005

| | Fasting status | | |
|---|---|---|---|
| | Fasting (n = 639) | Nonfasting (n = 522) | *P* |
| White blood cells (cells/μl) | 8056 | 8277 | 0.04 |
| Hematocrit (%) | 41.9 | 41.9 | 0.96 |
| Platelets (cells/μl) | 116.4 | 112.0 | 0.006 |
| Neutrophils (cells/μl) | 5132 | 6343 | 0.19 |
| Lymphocytes (cells/μl) | 1499 | 1446 | 0.11 |
| Monocytes (cells/μl) | 248 | 272 | 0.03 |
| Eosinophils (cells/μl) | 1074 | 1445 | 0.05 |

absolute monocyte count, absolute eosinophil count; and serum sodium, calcium, total protein, albumin, globulins, inorganic phosphate, LDH, AST, ALT, iron, cholesterol, or ESR.

## Discussion

Blood variables that varied significantly ($P < 0.01$) by fasting status in dolphins were compared with changes reported in patients with diabetes.[3,4,10,14,26] In addition to increased serum glucose, similarities between fasting dolphins and people with diabetes included decreased serum uric acid, increased GGT, increased platelet counts, increased alkaline phosphatase, and changes toward a more acidic metabolic state.

**Serum glucose.** Bottlenose dolphins have high serum glucose levels during the fasting state.[35,38] The present study, incorporating many more animals and samples, confirmed that dolphin glucose levels at 10 to 14 h of fasting are significantly ($P < 0.01$) higher than those obtained during the nonfasting state.

In previous studies, 72-h fasting experiments involving a limited number of bottlenose dolphins demonstrated an initial decline in serum glucose during the first 4 h after eating, followed by a sustained increase in glucose levels for 4 to 20 h, and a second decline in glucose between 20 and 48 h of fasting; glucose levels appeared to stabilize by 72 h.[38] Given these data, we anticipated that our reported serum glucose levels would have been lower if the study had involved blood samples from dolphins fasted 20 h or more. Indeed, decreasing serum glucose has been associated with decreasing serum glucagon in bottlenose dolphins after 24 h of fasting.[32]

Dolphins and other toothed whales (odontocete cetaceans) have large carrying capacities for glucose in the blood due to red blood cell glucose-transport systems.[7,11,12] Among terrestrial mammals, similar glucose-carrying capacities have been found only in humans and other primates.[18] Both primates and odontocete cetaceans have high encephalization quotients,[25] and positron emission tomography scans of living dolphins have revealed high levels of glucose consumption by the dolphin brain.[36] Both cetaceans and primates may have similar red blood cell glucose-transport systems due to high central nervous system glucose demands.[18] We hypothesize that evolution of a metabolic system that maintains high blood glucose during the fasting state could be advantageous in animals with anticipated periods of fasting and high brain-to-mass ratios.

**Uric acid, GGT, and alkaline phosphatase.** In our study, healthy fasting dolphins had significantly ($P < 0.01$) lower serum uric acid than did nonfasting dolphins. In humans with diabetes, decreasing serum uric acid has similarly been correlated with increasing fasting plasma glucose;[29] further, humans without diabetes demonstrate the opposite phenomenon (serum uric acid increases with increasing fasting plasma glucose). Hypouricemia (low serum uric acid) may occur in patients with diabetes due to renal tubular defects.[14] Significant increases in uric acid renal clearance are associated with poor glycemic control in humans with insulin-dependent type 1 diabetes;[16,17] this increase in uric acid renal clearance may specifically be due to abnormal primary sodium reabsorption in the proximal tubule, leading to renal distal tubular hyperfiltration in patients with diabetes.[15] Similar but transient renal tubular changes and potential hyperfiltration in bottlenose dolphins during the fasting state may explain a decrease in serum uric acid; the hypothesis of transient renal tubular changes in dolphins is supported further by a concurrent decrease in serum potassium during the fasting state compared with the nonfasting state.

Increased clearance of serum uric acid in diabetes can lead to increased uric acid in the urine. In addition to higher concentrations of urine uric acid in humans with diabetes, insulin resistance has been associated with low urinary ammonium and pH,[1] predisposing people with diabetes to uric acid renal calculi (kidney stones).[6,13,33] Similarly, uric acid renal calculi appear to be the most common abnormal renal finding in captive bottlenose dolphins.[27,34,37] Although the cause of uric acid renal calculi in dolphins has not been determined, a potential association with a diabetes-like condition in otherwise healthy dolphins warrants further investigation.

We report increased serum GGT in healthy, fasting bottlenose dolphins compared with healthy nonfasting bottlenose dolphins; significant ($P < 0.01$) increases in other hepatic markers (ALT, AST, and LDH) during the fasting state were not present. GGT has been identified as the primary hepatic marker predictor for type 2 diabetes in humans.[3,24] A dose-dependent association has been found between serum levels of GGT and the risk for developing either type 2 diabetes or impaired fasting glucose,[28] and subsequent studies have demonstrated increased or unchanged GGT levels over time correlated with increasing insulin resistance,[2] even within the normal human GGT range.[23] Oxidative stress and cellular stress related to insulin resistance may cause increased expression of GGT.[24]

In our study, fasting dolphins had significantly ($P < 0.01$) higher serum alkaline phosphatase levels than did nonfasting dolphins. Increasing blood glucose levels in patients with diabetes have increased levels of the bone isoenzyme of alkaline phosphatase;[39] the severity of diabetes and the presence of diabetic bone disease are associated.[26] A recent study suggested that the metabolic

**Table 3.** Comparisons (least squares means) of serum biochemical values of healthy *Tursiops truncatus* by fasting status, controlled for age group, gender, and number of samples submitted, Aug 1998–Dec 2005

| | Fasting status | | |
|---|---|---|---|
| | Fasting (n = 639) | Nonfasting (n = 522) | *P* |
| Glucose (mg/dl) | 112.4 | 108.0 | <0.0001 |
| Blood urea nitrogen (mg/dl) | 45.4 | 47.4 | <0.0001 |
| Creatinine (mg/dl) | 1.46 | 1.37 | <0.0001 |
| Uric acid (mg/dl) | 0.21 | 0.37 | <0.0001 |
| Sodium (mEq/l) | 155.5 | 155.2 | 0.01 |
| Potassium (mEq/l) | 3.67 | 3.79 | <0.0001 |
| Chloride (mEq/l) | 120.4 | 119.4 | <0.0001 |
| Carbon dioxide (mEq/l) | 23.1 | 24.2 | <0.0001 |
| Protein (g/dl) | 6.85 | 6.82 | 0.38 |
| Albumin (g/dl) | 4.25 | 4.23 | 0.12 |
| Globulins (g/dl) | 2.63 | 2.63 | 0.99 |
| Cholesterol (mg/dl) | 221.6 | 216.4 | 0.01 |
| Triglyceride (mg/dl) | 71.3 | 100.0 | <0.0001 |
| Calcium (mg/dl) | 9.16 | 9.07 | 0.02 |
| Inorganic phosphate (mg/dl) | 5.11 | 5.11 | 0.97 |
| Alkaline phosphatase (U/l) | 470.5 | 438.2 | <0.0001 |
| LDH (U/l) | 384.7 | 383.5 | 0.75 |
| AST (U/l) | 245.2 | 241.1 | 0.34 |
| ALT (U/l) | 33.6 | 32.9 | 0.44 |
| GGT (U/l) | 34.1 | 31.4 | 0.0007 |
| Iron (µg/dl) | 203.6 | 205.4 | 0.63 |
| CPK (mU/ml) | 135.6 | 127.3 | 0.0004 |
| ESR (60 min) | 9.0 | 9.0 | 0.20 |

state of diabetes affects the phenotype of osteoblasts, decreasing its response to bone-modulating hormones and leading to osteopenia.[31] The presence (or absence) of metabolic bone disease, specifically osteopenia or osteoporosis, has not been explored thoroughly in bottlenose dolphins.

**Platelet levels.** Healthy, fasting bottlenose dolphins had higher platelet levels than did nonfasting dolphins; no additional blood cell counts evaluated in the study differed significantly between the 2 study groups. Increased platelet levels and platelet hyperfunction are associated with diabetes, hyperglycemia, and potential complications of diabetes, including microangiopathy[9,21] and diabetic nephropathy.[40] High serum glucose has been demonstrated to increase platelet P-selectin expression and thrombin receptor-activating peptide induced fibrinogen binding by enhancing platelet reactivity to agonist stimulation.[41] The clinical relevance of increased platelet levels within normal ranges during a fasting state in dolphins has not been determined.

**Serum acid–base indicators.** Healthy, fasting dolphins had increased serum chloride levels and decreased carbon dioxide levels, supporting a more acidic metabolic state in fasting compared with that of nonfasting dolphins. The most common cause of metabolic acidosis in humans with diabetes, especially type 1 diabetes, is ketoacidosis;[42] abnormal serum chemistry changes during diabetic ketoacidosis include increased blood urea nitrogen. In our study, movement toward a more acidic metabolic state during the fasting phase in dolphins more likely is due to hyperfiltration and renal tubular changes than to ketoacidosis, because blood urea nitrogen levels decreased, not increased, during the fasting state. Ketones actually were reduced in dolphin blood samples taken at 24 h intervals during a 72-h fast.[35]

**High-protein diets.** The composition of a dolphin's diet may have an effect on the release of glucagon and subsequent increases in serum glucose after eating. Dolphins ingest high-protein diets with low to no carbohydrates. During 2005, the average daily dolphin diet fed at the MMP, excluding moisture content, consisted of 73.3% protein, 24.4% fat, and 2.2% carbohydrates from an estimated consistent average of 7 to 10 kg and 7000 to 13000 kilocalories of fish per day. MMP animals were fed a variety of fish types, including mackerel, capelin, herring, and squid. Interestingly, significant postprandial increases in glucagon release occur in healthy humans on low-carbohydrate diets as well as in humans with diabetes.[19] Further, improvements in glucose profiles and insulin sensitivity have been reported to occur in people with diabetes who ate a low-carbohydrate and high-protein diet over a 2-wk period.[5,30] We hypothesize that there may be important parallels between a dolphin's high-protein diet and evolution of a healthy diabetic-like state.

Limitations of our study include retrospective analysis of data not collected for the primary purpose of this research. For example, glucose values may vary due to sample-processing time—our samples were processed within 2 h after initial refrigeration. Although large sample sets can help control for such variation, future studies may elect to have stricter criteria for sample-processing time or more specific measurements of true circulating glucose (for example, measurements of glycosylated hemoglobin). In addition, the reference laboratory equipment used to

analyze samples was not developed specifically for processing dolphin blood. Throughout the 7 y study period, however, automatic analyzers were routinely calibrated before each use with standard controls, and the study was limited to results reported from a single laboratory. Further, the reference laboratory used in this study is the same laboratory that the MMP has used for over 20 y. Any variation related to reference laboratory results from true dolphin values would be consistent, allowing for valid comparisons of means between fasting and nonfasting animals. Finally, although animals in our study were categorized as fasting according to the time they were last fed, there is an ongoing potential for animals housed in the open ocean to eat wild, live fish between fed meals; on the basis of observations by trainers, the amount of wild, live fish ingested appears to be minimal in our population.

In summary, we report multiple parallels in hematologic and serum biochemical changes when comparing dolphins fasted for 10 to 14 h with humans with diabetes. Although previous studies have revealed that cetaceans and primates have similar central nervous system glucose demands and mechanisms for transporting high levels of glucose in the blood, the physiologic parallel between fasted dolphins and humans with diabetes had not been thoroughly characterized or explained previously. We hypothesize that there may be a common evolutionary reason, based on large brain size, for a diabetes-like state in mammals that is vestigial and pathologic in humans but remains active and essential in marine mammals.

Improving our understanding of how blood glucose levels are influenced by fasting, high-protein diets, large brain size, and high-fat body content in dolphins may provide valuable insight into the evolutionary cause of and treatments for diabetes in humans. Further, follow-up studies on the metabolism of bottlenose dolphins and subsequent potential health changes associated with feeding schedules or diet type may help to improve the health care of both captive and wild, stranded dolphin populations.

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