IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

The Relationship Between Diet, Plasma Glucose, And Cancer Prevalence Across Vertebrate.

Kumar Saurabh ,Research scholar ,Department of Zoology ,Sona Devi University Jamshedpur ,Jharkhand ,India.

Abstract

Birds have higher plasma glucose concentrations but lower cancer prevalence than other vertebrates. However, this inverse relationship between glucose and cancer may not hold within vertebrate groups. Given that diet affects blood sugar levels, and carnivores have higher cancer risk than herbivores, we also examined whether diet correlates with plasma glucose concentrations. We collected diet, mean plasma glucose concentration, and neoplasia data for up to 273 vertebrate species from existing databases. Across vertebrates, mean plasma glucose concentration negatively correlated with cancer prevalence, but that was mostly driven by differences in mean plasma glucose concentration and cancer prevalence between birds, mammals, and reptiles. Mean plasma glucose concentration was not correlated with diet across vertebrates nor with cancer prevalence within birds, mammals, or reptiles. Primary carnivores had higher neoplasia prevalence than herbivores when controlling for domestication. A hypothetical explanation for our results may be the evolutionary loss or downregulation of genes related to insulin-mediated glucose import in bird cells. This may have led to higher mean plasma glucose concentration, lower intracellular glucose concentrations in the form of glycogen, and production of fewer reactive oxygen species and inflammatory cytokines, potentially contributing to lower neoplasia prevalence in extant birds compared to mammals and reptiles.

Keywords: Plasma, glucose, vertebrates, carnivores, neoplasia, insulin-mediated, evolutionary, intracellular, insulin-mediated, glycogen, inflammatory cytokines, cancer, production.

Introduction

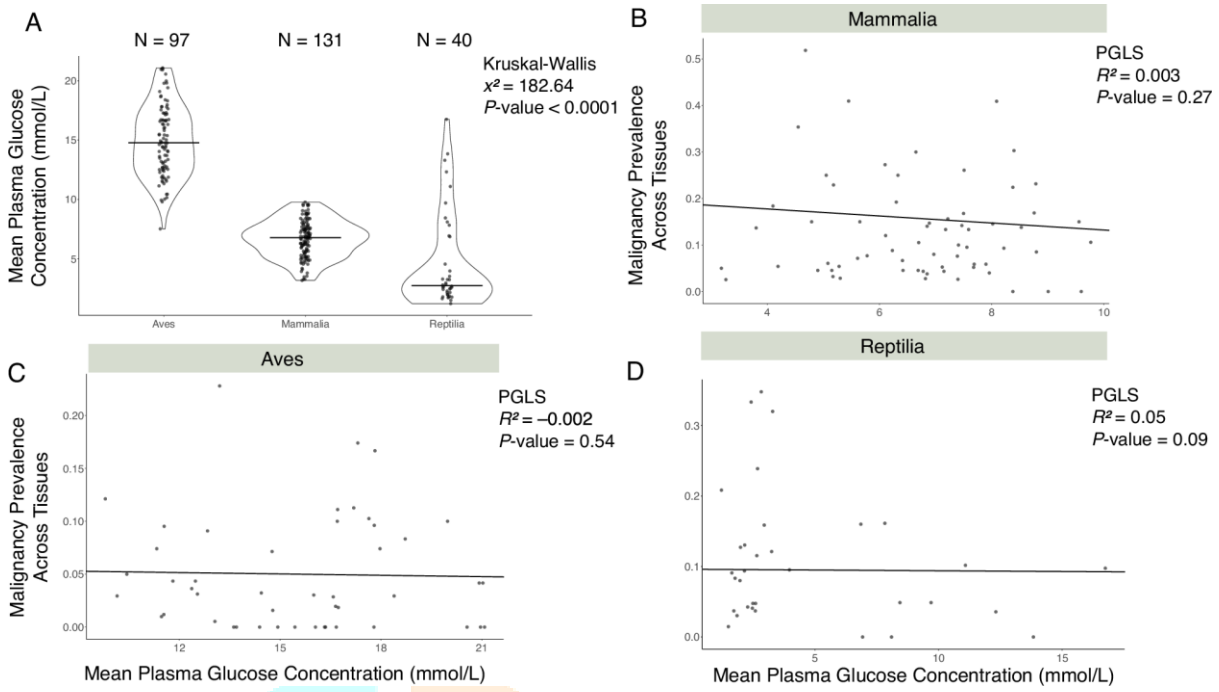
Explaining patterns of cancer susceptibility among multicellular organisms is a major challenge in comparative oncology. There is extensive evidence that diet affects cancer risk in humans[1,2,3]. Recently, researchers have begun investigating the role of diet in species' susceptibility to cancer. Vinzce et al.[4] have demonstrated that mammals that eat vertebrate meat or mammalian meat have more cancer-related deaths. Also, within mammals[5,6] and across vertebrates[7], higher trophic levels have higher cancer and neoplasia prevalence. Birds have higher plasma glucose concentration than other vertebrates[8,9,10] (150–300% higher than mammals of similar body size[8]) and less cancer than mammals and reptiles[6,11]. What is the relationship between diet, plasma glucose levels, and cancer across vertebrates, and could it help explain why birds get less cancer than mammals and reptiles?

Glucose is a unifying factor among a number of risk factors for cancer prevalence across species, including larger litter/clutch size[12,13] and carnivorous diet[4,7]. There is conflicting evidence, however, about an association between diet and blood glucose levels in the literature. In humans[14], common voles (*Microtus arvalis*), tundra voles (*Alexandromys oeconomus*)[15,16], and vampire bats (*Desmodus rotundus*)[17], dietary components, such as micronutrients and macronutrients, or food deprivation, can change blood glucose levels. Birds, such as Noisy miners (*Manorina melanocephala*), that eat nectar and fleshy fruits have higher plasma glucose levels than birds, such as Welcome swallows (*Hirundo neoxena)*, that eat insects[18,19]. Across 160 passerine bird species, the species that eat mostly fruit and nectar have

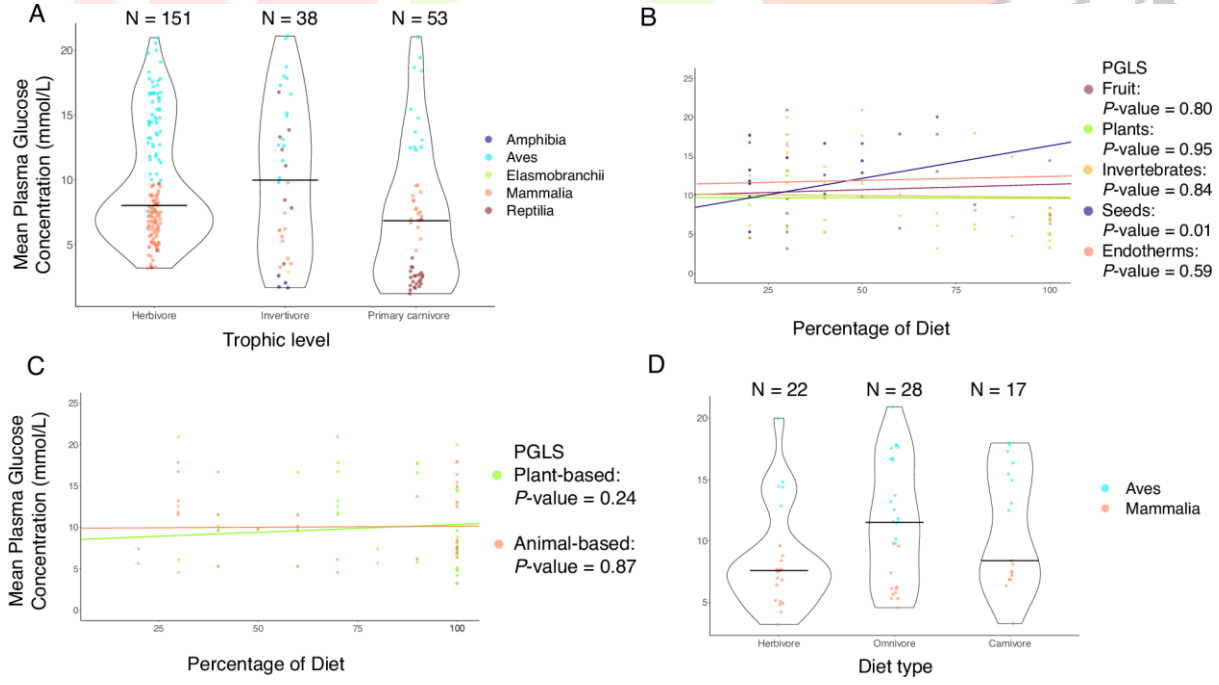
higher blood glucose concentrations than other passerine species[20]. Fish, such as sea bass (*Dicentrarchus labrax*), brown trout (*Salmo trutta fario*), and dogfish (*Squalus acanthias*) have lower blood glucose levels after fasting for a few days[21]. Yet mammals like cats (*Felis catus*) and rats (*Rattus norvegicus domestica*)[22], the great fruit-eating bat (*Artibeus lituratus*), and the Jamaican fruit bat (*Artibeus jamaicensis*)[23], maintain their blood glucose levels during fasting. Other studies in birds show that regardless of diet and the frequency of eating, blood glucose concentrations remain fairly constant[24], with no detectable differences in blood glucose concentrations between herbivorous, omnivorous, or insectivorous songbirds[25]. Also, many other fish species have stable blood glucose concentrations when starving[21]. Within individual humans and model organisms, increased levels of glucose in the blood are associated with increased oxidative stress, DNA damage, glycated proteins, and inflammation, all of which could increase cancer risk and development[26,27,28,29,30,31,32]. Studies in birds have found a positive correlation between blood glucose levels and species clutch size[20,25], and a positive correlation between clutch size and cancer prevalence[12]. Over evolutionary time we would expect that species with relatively higher blood glucose concentrations would have evolved adaptations preventing these pro-carcinogenic properties[8,33,34,35], leading to a decoupling of cancer prevalence from glucose concentrations. Thus, we might predict no correlation between plasma glucose concentration and cancer prevalence across vertebrates. However, there may be various unknown confounding variables affecting the association between plasma glucose concentration and cancer prevalence over millions of years of evolution. If we form our hypothesis based on the broadly available data of current vertebrates, we would expect a negative correlation between plasma glucose concentration and neoplasia prevalence across vertebrates. This is because data on extant species show that birds are the taxon with the highest plasma glucose concentration relative to other vertebrate taxa[8,9,10] and have less cancer mortality than mammals and reptiles[6,11]. Mechanistic support for this hypothesis comes from the fact that extant birds, versus mammals, lack in most of their tissues the GLUT4 protein[8,36] that imports glucose into cells, they have higher energy expenditures and have adapted to thrive on fatty acids rather than glucose[37,38,39]. Also, extant birds produce fewer reactive oxygen species via mitochondrial respiration in comparison to mammals and reptiles[40], there are higher levels of the antioxidant uric acid in birds than mammals[41,42], and the antioxidant NRF2 is constitutively expressed in most birds[35]. Thus, based on data across extant vertebrate species we might expect a negative correlation between plasma glucose levels and cancer prevalence.

In this study we test for three associations across vertebrate species. Firstly, we test for a relationship between diet and mean plasma glucose concentration. Although one of the largest studies to date on diet and plasma glucose levels across 160 bird species has shown that eating nectar and fruits, versus insects, is associated with higher plasma glucose levels[20], no other study has tested correlations between diet and plasma glucose concentrations across vertebrates. Secondly, we test for a relationship between neoplasia prevalence and mean plasma glucose concentration. Thirdly, we test for a relationship between neoplasia prevalence and different ways of categorizing diet: (a) trophic level (herbivore, invertivore, primary carnivore, and secondary carnivore), (b) percentage of food type in the diet (fruit, invertebrates, plant, seeds, vertebrate ectotherms, vertebrate endotherms, animal-based, plant-based), and (c) overall diet type (herbivore, omnivore, carnivore), with or without controlling for mean plasma glucose concentration and domestication. Even though the associations between trophic level and neoplasia prevalence have been previously studied across vertebrates[7], we reevaluate previous results in a subset of species for which we had plasma glucose data and examine the unknown association between diet and neoplasia when controlling for mean plasma glucose concentration and domestication across vertebrates. We test these associations using literature resources on diet, Species360 data on glucose concentrations in the plasma, and neoplasia prevalence data from up to 273 species. Here, we show that there is: (1) no correlation between diet and mean plasma glucose concentration across vertebrates; (2) a negative correlation between cancer prevalence and mean plasma glucose concentration across vertebrates but not within birds, mammals, or reptiles; (3) higher neoplasia prevalence in primary carnivores than herbivores when controlling the analysis for species domestication.

Result



A Mean plasma glucose concentrations are relatively higher in Aves than Mammalia and Reptilia (Kruskal–Wallis test; P-value < 0.0001; degrees of freedom = 2). There is no correlation between mean plasma glucose concentration and malignancy prevalence across tissues for B 66 mammalian species, C 47 bird species, and D 33 reptile species. The statistical tests were two-sided. P-values have not been adjusted for FDR corrections. The P-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 3–5. The outlier species (Rosner's test) with the highest malignancy prevalence are: Didelphis virginiana in panel (B) Gallus gallus in panel (C) and Lampropeltis triangulum, Lampropeltis getula, and Pituophis catenifer in panel (D) from top to bottom. PGLS phylogenetic generalized least squares.



A Trophic level is not correlated with mean plasma glucose concentrations across 242 species (PGLS: P-value ≥ 0.05; Supplementary Data 1). B There was no correlation between the percentage of fruit, plants, invertebrates, seeds, or endothermic vertebrates (Endotherms), and mean plasma glucose concentrations for 20, 34, 27, 17, or 10 species, respectively, after correcting for multiple testing. C The percentage of plant-based foods or animal-based foods in a species' diet was not correlated with mean plasma glucose concentrations for 47 or 38 species, respectively (PGLS: P-value > 0.05). D Diet type is not correlated with mean plasma glucose levels for 67 species (PGLS: P-value > 0.05; Supplementary Data 1). The

horizontal black line in each diet category shows the mean plasma glucose concentration in that trophic (plot A) or diet category (plot D). In D, herbivores refer to animals that have a 100% plant diet, omnivores refer to animals that have >0% plant and meat diet, and carnivores refer to animals that have a 100% meat (invertebrate or vertebrate) diet. The statistical tests were two-sided. P-values have not been adjusted for FDR corrections. The P-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 1. Each dot shows the mean plasma glucose concentration and diet category of one species. N shows the number of species per diet category (plots A & D).

Conclusion

Our results suggest that the differences in mean glucose concentration in birds relative to other vertebrates are unrelated to the lower cancer prevalence in birds. This is consistent with Satoh's description on the divergence of birds versus mammals and reptiles during the Permian-Triassic boundary35. Future studies should test the hypothesized mechanisms of cancer suppression in birds, and perhaps explore how they might be translated to human cancer prevention. The rise of comparative phylogenomics80,81 can also bring insights into how particular glucose-transport-related genes and pathways are associated with cancer-related genes and pathways across the animal kingdom. These approaches will bring us closer to explaining the diversity of cancer prevalence across species and developing interventions that might help us live like a bird.

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