International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn23235

The use of assistance dogs in the detection of hypoglycemic episodes in type 1 diabetes: a descriptive and comprehensive review

Anna Luiza Alves Boldrin de Siqueira[1], Gisleide Tristão Franco de Alcântara[1], Julia Maria Mendes Peloi[1], Guilherme Eugênio Gil[1], Jesselina Francisco dos Santos Haber[1*]

[1] UNIMAR - University of Marilia (Faculty of Medicine), Marilia, Sao Paulo, Brazil.

*Corresponding Author: Dr. Jesselina Francisco dos Santos Haber,
University of Marilia (Faculty of Medicine), Marilia, Sao Paulo, Brazil.
E-mail: haber.jesselina@gmail.com
DOI: https://doi.org/10.54448/ijn23235
Received: 05-10-2023; Revised: 07-11-2023; Accepted: 07-12-2023; Published: 07-13-2023; IJN-id: e23235

Abstract

Introduction: Type 1 diabetes mellitus (T1DM) is a disease of autoimmune and polygenic origin, characterized by the destruction of the beta cells of the pancreatic islets and, consequently, the absence of insulin production. The treatment aims at imitating the physiological secretion of insulin in individuals without comorbidity, using insulin therapy. Hypoglycemia is defined as any event of abnormally low blood glucose, putting the person at potential risk. Tachycardia, tremors, pallor, cold sweating, lingual paresthesia, and blurred vision, possibly leading to coma, are its main signs and symptoms. The recognition of serious clinical conditions transmitted by both visual and olfactory signals can be understood and elaborated by the dog's cognitive system, allowing the rapid detection of a hypoglycemic episode and, thus, allowing adequate conduct before a serious episode. **Objective:** To analyze the advances, both in studies and in professional practices, in the use of assistance dogs to identify hypoglycemia in diabetics 1, as well as to seek to understand the consequences of unidentified and untreated hypoglycemia. **Methods:** The most relevant studies searched using the keywords "hypoglycemia AND diabetes", in addition to "diabetes alert dogs" in Google Scholar, were analyzed, with 4 corresponding to the objectives of the current research. Finally, pathology books and official documents from the Ministry of Health and the Brazilian Society of Diabetes were used to build a theoretical explanation. **Results and Discussion:** Dogs are conditioned to respond with specific alert behaviors, such as barking or licking, when levels of their owner's blood sugar levels are below the ideal range, as identified by the amount of isoprene released in the individual's breath. This attitude causes the patient to measure his plasma glucose level, helping him to carry out the appropriate measures to keep the levels back to normal. The hesitation of the occurrence of hypoglycemia causes some type 1 diabetic to contain their lifestyle to try to reduce the probability of the occurrence of a hypoglycemic episode, negatively affecting their quality of life and psychological well-being. In addition, they can intentionally maintain hyperglycemia to avoid a sudden drop in glucose, however, this practice results in late problems such as nephropathy, neuropathy, and cardiopathy. Conclusions: Hypoglycemia is one of the main threats for people with diabetes, as it results in severe symptoms that can lead to coma if not treated quickly. Possibly, dogs perceive plasma glycemic variations using, in addition to the olfactory apparatus, perceptions captured through other senses, mainly vision, but the scarcity of studies carried out with dogs trained to support people with diabetes problems, mainly in Brazil, makes the efficiency of these animals to detect alterations of glucose in the blood remains debatable.

Keywords: Type 1 diabetes mellitus. Working Animals. Hypoglycemia.

Introduction

Type 1 diabetes mellitus

Diabetes mellitus is a group of metabolic diseases responsible for causing persistent hyperglycemia. It is the result of defects in the secretion and/or action of insulin that involve specific pathogenic processes, such as the destruction of pancreatic beta cells, resistance to insulin action, disorders of insulin secretion, among

others. It is a common disease with increasing prevalence, especially in developing countries. According to the 2005 Brazilian Institute of Geography and Statistics (IBGE), 11% of the population aged 40 years or older have diabetes, which represents about 5.5 million individuals **[1]**.

Type 1 diabetes mellitus (T1DM) is a disease of autoimmune and polygenic origin, characterized by the destruction of the beta cells of the pancreatic islets and, consequently, the absence of insulin production **[2]**. Formerly known as insulin-dependent diabetes mellitus, juvenile diabetes or with a tendency to ketosis, the disease occurs with greater prevalence in children, adolescents and young adults, and there is no discrepancy in the number of cases between males and females **[3]**.

The classic clinical picture is composed of polyuria, polydipsia, polyphagia and weight loss, and nausea, weakness, fatigue and mood swings may also be present **[4]**. The diagnostic criteria adopted by the Brazilian Society of Diabetes (SBD) are fasting blood glucose ≥ 126mg/dL, in two exams, oral glucose tolerance test ≥ 200mg/dL, in two exams, glycated hemoglobin ≥ 6.5%, in two tests or random blood glucose ≥ 200mg/dL associated with the classic clinical picture **[2]**.

The laboratory presence or absence of circulating autoantibodies, such as anti-islet antibody, anti-insulin autoantibody, anti-glutamic acid decarboxylase antibody (anti-GAD65), anti-tyrosine phosphatase antibody IA-2 and IA-2B, and anti-zinc transporter antibody, allows their classification into subtypes. Subtype 1A is the most frequent in the population, and the presence of these antibodies is confirmed in laboratory tests. Subtype 1B is defined by its idiopathic nature, but the treatment and risks of chronic complications are not different from 1A **[2]**.

Treatment is aimed at mimicking physiological insulin secretion in individuals without the comorbid condition. Therefore, the medication used is insulin therapy, mimicking basal and prandial secretion. Long-acting (glargine U100, detemir) and ultra-long-acting (glargine U300 and degludec) analogues are recommended as a baseline component, due to the lower incidence of hypoglycemia. In turn, short-acting human subcutaneous insulin (regular), rapid-acting insulin analogues (lispro, aspart and glulisine) and ultra-rapid-acting insulin analogues (ultrarapid aspart and inhalable technosphere) are used for 15 to 20 minutes before meals, avoiding postprandial hyperglycemia **[5]**.

Glycemia Monitoring

To avoid macro and microvascular complications, good glycemic control is necessary as part of diabetic treatment. For this evaluation, glycated hemoglobin (HbA1c), daily capillary blood glucose levels, the standard deviation of the mean blood glucose and the time within the recommended blood glucose target are used, in addition to tests such as postprandial blood glucose, fructosamine, 1,5-anhydroglucitol (1,5-AG) and glycated albumin **[2]**.

Glycated hemoglobin (HbA1c), the gold standard test for analyzing metabolic control, allows the estimation of blood glucose levels in the last 3 to 4 months. This occurs because blood glucose irreversibly binds to hemoglobin during the life span of the red blood cell, which is 120 days. The values of this test vary between scientific societies, but most have a consensus that the value should be < 7%, equivalent to an estimated mean blood glucose of 154 mg/dL **[2]**.

Self-monitoring of blood glucose shows blood glucose data in real time, helping to reduce the risk of ketoacidosis and hypoglycemia. Glycemic targets vary during the fasting or preprandial period from 70 to 130 mg/dL and in the postprandial period from 90 to 180 mg/dL. Due to this variation during the day, it is recommended to monitor blood glucose five times a day (before main meals and 2 hours after each of them). In addition to identifying acute complications, it allows the doctor and patient to devise strategies to correct and avoid offtarget glycemia, according to the insulin/carbohydrate ratio, in addition to allowing adjustments in basal insulin **[2]**.

Hypoglycemia

The Working Group on Hypoglycemia of the American Diabetes Association (ADA) conceptualizes hypoglycemia as any abnormally low blood glucose event that puts a person at potential risk. Whipple's Triad is the set of clinical manifestations that occur during an episode of low plasma glycemia signs and symptoms compatible with hypoglycemia, biochemical confirmation and resolution of the occurrence after glycemic replacement **[6]**.

The causes are diverse and may not always cause hypoglycemia right away. Delay in feeding and error in counting the insulin dose are the most frequent. The practice of physical activity promotes late hypoglycemia, as well as alcohol abuse, responsible for impairing counter-regulation by blocking hepatic gluconeogenesis **[1]**.

Also, hypoglycemic symptoms, despite varying between individuals, as well as in the same individual depending on surrounding factors such as sleep and stress, are related to the time of the glycemic drop, as well as its effects on the autonomic nervous system. When this drop is rapid, neurogenic symptoms prevail,

produced by the activation of the Central Nervous System with a consequent increase in the secretion of glucagon and adrenaline, causing tachycardia, palpitations, tremors, pallor, cold sweating and hunger. When the descent occurs more gradually, there is a predominance of neuroglycopenic symptoms, such as confusion, headache, lingual paresthesia, blurred vision and catatonia, which can lead to coma **[7]**.

The glycemic threshold of 70 mg/dL is adopted by the ADA, allowing the classification of hypoglycemia into five groups, namely severe hypoglycemia, documented symptomatic, probable symptomatic, asymptomatic and relative hypoglycemia. The first is the only one that happens when the diabetic himself is not fully aware of administering glucose or other corrective actions in the face of the situation **[6]**.

Besides, symptomatic hypoglycemia presents the typical signs and symptoms, being differentiated only when there is documentation of glycemia below 70 mg/dL. classifying it as documented symptomatic, or, when there was no measurement of plasma glucose, but its low value is assumed due to clinical manifestations, which is the case of probable symptomatic **[6]**. In this sense, asymptomatic hypoglycemia is characterized by a monitored glycemic value below 70 mg/dL with clinical absence. The relative, in turn, has plasma glucose documentation above the threshold value, however, it presents the signs and symptoms described. The latter is more commonly described by individuals who remained for so long with high blood glucose levels that the limits of adrenergic and symptomatic responses were naturally modified **[6]**.

The treatment of this complication consists of raising plasma glucose to values between 80 and 100 mg/dL. There are three phases to be followed (acute intervention, maintenance therapy and subsequent measures), and mild to moderate hypoglycemia can be treated on an outpatient basis, while severe cases require third-party assistance with in-hospital evaluation **[6]**. The correction must be made with 10 to 20 grams of simple carbohydrates (equivalent to 2 teaspoons of sugar or 100 ml of soda or 2 candies) and, if necessary, repeat every 15 minutes. When the patient is conscious, he is able to ingest it himself, but if swallowing is not possible, it is necessary for another person to inject glucagon by subcutaneous or intramuscular injection. If the injection is not possible, sugar or honey should be placed sublingually or between the gum and the cheek and the individual should be taken to a health service **[1]**.

Alert Dogs - Hypoglycemia

The ability to identify volatile organic compounds is due to genetic, anatomical, and physiological differences in the canine olfactory system. The number of olfactory receptors, compared to humans, is 20 times greater, reaching 220 million, allowing a more efficient cognitive analysis of chemosensory information. Therefore, it is not uncommon to see them involved in biosecurity, drug enforcement, food security, prevention, and containment of bio and agroterrorism **[8]**.

The most recognized application in the field of medicine is the detection of cancer, however, its ability to perceive chemical changes and even expressions in the human body, often associated with plasma glycemic variations, is being increasingly studied. The case that began to generate interest in the use of diabetes alert dogs began in 2003, when Armstrong's Labrador was trained, by Mark Ruefenacht (USA), to sniff out subtle chemical changes, and then be able to alert the owner about the episode of hypoglycemia **[8]**.

The first scientific study of dogs alerting their diabetic owners to potentially harmful glycemic states was published by Wells et al., in 2008 **[9]**. In this article, over 65% of subjects indicated that dogs exhibited behavioral reactions during at least one hypoglycemic event, whereas one-third of dogs reacted to the vast majority of episodes, indicated primarily by barking, licking, and nose rubbing. In addition, 33% of owners indicated that their dogs exhibited these behaviors even before the individual recognized the hypoglycemic state. From 2013 to 2017, other studies investigated the dog's efficiency in alerting their owners about episodes of hypoglycemia or hyperglycemia, reaching a variability in sensitivities and specificities of 0.29–0.80 and 0.49–0.96, respectively **[9]**.

It is proven that the canine olfactory apparatus has a great role in the identification of several organic compounds generated in certain diseases (especially cancer, seizures, and infectious and psychiatric diseases). In a recent study, Saidi et al. collected respiratory samples from six diabetic patients compared with those from non-diabetic individuals, the former having increased concentrations of benzaldehyde, toluene, methane, aniline, and carbonchloric acid. During hypoglycemia, isoprene is mainly released, along with ketones (eg, acetone and acetaldehyde), hydrocarbons (ethane, pentane, and isoprene), acetaldehyde, methanol, and ethanol **[10]**.

In addition to sensitivity to the smell of organic compounds, dogs can differentiate between facial expressions, changes in voice pitch, and sudden shifts in attention or posture. Therefore, the recognition of serious clinical conditions transmitted by both visual and olfactory signals can be understood and elaborated by the dog's cognitive system **[11]**.

Because of this, the present study carried out a

literature review to analyze the advances, both in studies and in professional practices, of the use of assistance dogs for the identification of hypoglycemia in diabetics 1, as well as seeking to understand what are the consequences of hypoglycemia unidentified and untreated.

Methods

Study Design

A descriptive and comprehensive literary review was carried out, selecting studies carried out from 2007 to 2023.

Search Strategy and Literary Source

For the bibliographic sources, the most relevant studies searched using the keywords "hypoglycemia AND diabetes", in addition to "diabetes alert dogs" in Google Scholar, Scopus, PubMed, Scielo, and Web of Science, were analyzed, with 4 corresponding to the objectives of the current search. Finally, pathology books and official documents from the Ministry of Health and the Brazilian Society of Diabetes were used to build a theoretical explanation.

Results and Discussion

The articles used in this work indicate that there are different definitions of hypoglycemia based on plasma glucose levels, devices used, and the impact of hypoglycemia on the patient. Mild hypoglycemias interfere with day-to-day activities, such as driving, while severe episodes require third-party intervention and, if not treated, can be fatal **[10,11]**.

The hesitation of the occurrence of hypoglycemia causes some type 1 diabetic to contain their lifestyle to try to reduce the probability of the occurrence of a hypoglycemic episode, negatively affecting their quality of life and psychological well-being. In addition, they can intentionally maintain hyperglycemia to avoid a sudden drop in glucose, however, this practice results in late problems such as nephropathy, neuropathy, and heart disease **[8-11]**.

Studies suggest that certain pet dogs naturally react to their owner's hypoglycemic state, and based on this, institutions have begun to train dogs to live with and help people with type 1 diabetes. Just like dogs trained to detect drugs, they are conditioned to respond with specific alerting behaviors, such as barking or licking, when their owner's blood sugar levels are below the ideal range. This attitude of the pet causes the patient to measure his plasma glucose level, helping him to carry out the appropriate measures to keep the levels back to normal **[9-11]**.

Isopropene, one of the most common volatile compounds in human breath, is increased in hypoglycemic episodes, which could explain the olfactory recognition by dogs of the drop in glucose. However, its endogenous source is undetermined, being defined only as a byproduct of cholesterol biosynthesis. A plausible reason for its increase is that, during hypoglycemia, the exacerbated release of isoprene would be due to tachycardia and increased blood flow **[11,12]**.

Each human being has a characteristic odor, to which the animal is accustomed and, together with the progressive decline in the ability to detect odor over the years, can generate alerts of false negatives and false positives, which can reassure or generate false concerns about a normal state of the patient **[12-14]**. The evaluation of the quality of the olfactory performance of dogs is still little explored, because of this, it is necessary to define operational procedures that allow the continuous monitoring of the performance of your dogs, such as verifying the accuracy of glucose meters **[15-20]**.

Conclusion

Hypoglycemia is one of the main threats for people with diabetes, as it results in severe symptoms and can lead to coma if not treated quickly. However, the patient must have cognitive and functional capacity, both to identify and to correct it, since many interventions are invasive, through finger pricks or installation of sensors, in addition to high financial values for more expensive devices current. Assistance dogs offer a non-invasive way to detect episodes, both hyper and hypoglycemic, allowing their owner to be alert while still being able to act without help from others. Possibly, dogs perceive plasma glucose variations using, in addition to the olfactory apparatus, perceptions captured through other senses, mainly vision. The scarcity of studies carried out with dogs trained to support people with diabetes problems, mainly in Brazil, means that the efficiency of these animals to detect changes in blood glucose remains questionable. However, even if they cannot replace monitoring through self-testing, they can be seen as an aid in the treatment, since their presence promotes healthy lifestyles, such as going out for a walk, in addition to psychological benefits, promoting an improvement in the quality of life and glycemic control of diabetics.

Acknowledgement

Not applicable.

Ethical Approval
Not applicable.

Informed consent
Not applicable.

Funding
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

References
1. Brazil. Ministry of Health. Secretary of Health Care, Department of Primary Care. Diabetes Mellitus. Virtual Health Library (VHL). Brasilia: Ministry of Health, 2006. Available at: <https://bvsms.saude.gov.br/bvs/publicacoes/diabetes_mellitus.PDF>. Accessed on: 01 Mar. from 2023.
2. SBD – Brazilian Society of Diabetes. Guidelines of the Brazilian Society of Diabetes 2019-2020. Clannad, 2019. Available at: <https://www.saude.ba.gov.br/wpcontent/uploads/2020/02/Diretrizes-Sociedade-Brasileira-de-Diabetes-20192020.pdf>. Accessed on: 25 Feb. 2023.
3. Cotran SR, Kumar V, Robbins SL. Pancreas. Basic pathology. 5. ed. Rio de Janeiro: Guanabara Koogan. 1994. Chap. 17.
4. Brazil. Ministry of Health. Diabetes. Virtual Health Library (VHL). Jun. 2009. Available at: <https://bvsms.saude.gov.br/diabetes/>. Accessed: 25 Feb. from 2023.
5. Junior WSS, Gabbay MAL, Lamounier RN. Insulin therapy in type 1 diabetes mellitus (DM1). Official Guideline of the Brazilian Society of Diabetes (2022). Jan, 2022. Available at: <https://diretriz.diabetes.org.br/insulinoterapia-no-diabetes-mellitus-tipo1-dm1/>. Accessed on: 26 Feb. from 2023.
6. Oliveira AMP, Gomes MLV. Diabetes mellitus and hypoglycemia. Scientific Area of Endocrinology. Faculty of Medicine of the University of Coimbra. Feb, 2014. Available at: < https://core.ac.uk/reader/43574820>. Accessed on: 01 Mar. from 2023.
7. Gallego R, Caldeira G. Acute complications of diabetes mellitus. Portuguese Journal of General and Family Medicine. Vol. 23, nº5, pp 565-575, Sept. 2007. Available at: <https://www.rpmgf.pt/ojs/index.php/rpmgf/article/view/10406/10142>. Accessed on: 01 Mar. from 2023.
8. Lippi G, Plebani M. Diabetes alert dogs: a narrative critical overview. Clin Chem Lab Med. 2019 Mar 26;57(4):452-458. doi: 10.1515/cclm-2018-0842.
9. Wells DL, Lawson SW, Siriwardena AN. Canine responses to hypoglycemia in patients with type 1 diabetes. J Altern Complement Med. 2008 Dec;14 (10):1235-41. doi: 10.1089/acm.2008.0288.
10. Reeve C, Cummings E, McLaughlin E, Smith S, Gadbois S. An Idiographic Investigation of Diabetic Alert Dogs' Ability to Learn From a Small Sample of Breath Samples From People With Type 1 Diabetes. Can J Diabetes. 2020 Feb;44 (1):37-43.e1. doi: 10.1016/j.jcjd.2019.04.020.
11. Weber KS, Roden M, Müssig K. Do dogs sense hypoglycaemia? Diabet Med. 2016 Jul;33(7):934-8. doi: 10.1111/dme.12975.
12. Kokocińska-Kusiak A, Woszczyło M, Zybala M, Maciocha J, Barłowska K, Dzięcioł M. Canine Olfaction: Physiology, Behavior, and Possibilities for Practical Applications. Animals (Basel). 2021 Aug 21;11(8):2463. doi: 10.3390/ani11082463.
13. Reeve C, Wilson C, Hanna D, Gadbois S. Dog Owners' Survey reveals Medical Alert Dogs can alert to multiple conditions and multiple people. PLoS One. 2021 Apr 14;16(4):e0249191. doi: 10.1371/journal.pone.0249191.
14. Rooney NJ, Guest CM, Swanson LCM, Morant SV. How effective are trained dogs at alerting their owners to changes in blood glycaemic levels?: Variations in performance of glycaemia alert dogs. PLoS One. 2019 Jan 15;14(1):e0210092. doi: 10.1371/journal.pone.0210092.
15. Wilson C, Morant S, Kane S, Pesterfield C, Guest C, Rooney NJ. An OwnerIndependent Investigation of Diabetes Alert Dog Performance. Front Vet Sci. 2019 Mar 27;6:91. doi: 10.3389/fvets.2019.00091.

16. Behrend E, Holford A, Lathan P, Rucinsky R, Schulman R. 2018 AAHA Diabetes Management Guidelines for Dogs and Cats. J Am Anim Hosp Assoc. 2018 Jan/Feb;54(1):1-21. doi: 10.5326/JAAHA-MS-6822.
17. Gonder-Frederick LA, Grabman JH, Shepard JA. Diabetes Alert Dogs (DADs): An assessment of accuracy and implications. Diabetes Res Clin Pract. 2017 Dec;134:121130. doi: 10.1016/j.diabres.2017.09.009.
18. Lippi G, Cervellin G, Dondi M, Targher G. Hypoglycemia Alert Dogs: A Novel, Costeffective Approach for Diabetes Monitoring? Altern Ther Health Med. 2016 Nov;22(6):14-18. PMID: 27866176.
19. Petry NM, Wagner JA, Rash CJ, Hood KK. Perceptions about professionally and nonprofessionally trained hypoglycemia detection dogs. Diabetes Res Clin Pract. 2015 Aug;109(2):389-96. doi: 10.1016/j.diabres.2015.05.023.
20. Los EA, Ramsey KL, Guttmann-Bauman I, Ahmann AJ. Reliability of Trained Dogs to Alert to Hypoglycemia in Patients With Type 1 Diabetes. J Diabetes Sci Technol. 2017 May;11(3):506-512. doi: 10.1177/1932296816666537.