Opinion Paper

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Diabetes alert dogs: a narrative critical overview

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Abstract: Owing to their virtually incomparable olfactory apparatus and the mutual loving relationship with man, the use of dogs for assisting humans in many activities has become commonplace. Dogs have been used for long for livestock herding, hunting and pulling. More recently, they have been employed for servicing or assisting people with disabilities, for rescuing, for pet therapy and, last but not least, for detecting a vast array of volatile organic compounds related to drugs, narcotics, explosives and foods. Although cancer detection seems the most distinguished use of "man's best friends" in science and medicine, increasing emphasis is being placed on their capacity to perceive chemical changes or human expressions associated with harmful, even life-threating, blood glucose variations. The evidence available in the current scientific literature attests that diabetes alerting dogs (DADs) have a heterogeneous efficiency for warning owners of episodes of hypoglycemia or hyperglycemia, with sensitivities and specificities ranging between 0.29–0.80 and 0.49–0.96, respectively. Although the adoption of DADs seems effective for improving the quality of life of many diabetics patients, some important drawbacks can be highlighted. These typically include adoption and keeping expenditures, lack of certification or accreditation of dog providers, poor harmonization of training procedures, significant inter-breed, intra-breed and intra-dog variabilities, wide-ranging alert behaviors, ability of owners to identify dog's alerts, as well as lack of quality assessment of a dog's "diagnostic" performance. Overcoming many of these limitations shall probably make DADs more efficient tools for improving diabetes management.

Keywords: diabetes; dogs; hyperglycemia; hypoglycemia.

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Introduction

Domestic dog, a member of the genus *Canis* (canines), was the first animal to be domesticated by humans, and is now universally regarded as the "man's best friend" [1]. Besides being widely used as pets, dogs also help humans in many activities, thus assuming the conventional nickname of "working dogs". The most common tasks performed by dogs include activities as old as their domestication (e.g. livestock herding, hunting and pulling), more recent tasks (servicing or assisting people with various forms of disability, for rescuing or for pet therapy), along with a series of activities directly attributable to their incomparable sniffing capacity.

The canine olfactory system, which is probably the most developed after that of wolves and bears [2], gives them the capacity to detect even negligible amounts of volatile organic compounds (VOCs) related to drugs, narcotics, explosives and foods. Hence, it is commonplace to see dogs involved in biosecurity, drug enforcement, food security, prevention and containment of bio- and agroterrorism. Ideally, dogs' efficiency to search target odors make them excellent "tools" for rapid and efficient target recognition. As a matter of fact, canine olfactory perception is vastly more sensitive than the human sense of smell. This is mostly due to a number of genetic, anatomic and physiological differences, allowing dogs to more efficiently record and cognitively analyze chemosensory information present in the environment [3]. Several lines of evidence now attest that the genetics of olfactory receptor apparatus has been subjected to considerable expansion and contraction throughout mammal evolution, thus resulting in an enormous molecular, biochemical, anatomic and function heterogeneity [2]. The overall area including olfactory cells is approximately 5 cm^2 in human nose, whilst is over 20-fold larger in dogs (i.e. usually comprised between 150 and 170 cm^2), so that the final number of olfactory receptors is >20-fold higher in dogs than in humans (i.e. ~5 vs. ~220 million) [3].

This virtually incomparable smelling capacity has contributed to broaden the use of dogs to many detection applications, including disease recognition. Albeit the most known relevance of these friendly animals in science and medicine is cancer detection [4, 5], increasing

Figure 1: Armstrong, *Guinness Book of World Records* entrant for being capable of warning his owner of the risk of a hypoglycemic episode.

emphasis is now being placed on their capacity to perceive chemical (and perhaps expression) changes in human body often associated with remarkable variations of blood glucose concentration. With specific training, a dog may hence be able to warn its owner on both hypoglycemic and hyperglycemic episodes. The relative short story of diabetes alerting dogs (DADs) probably commenced in the 2003 when Armstrong, a yellow Labrador Retriever, received an outstanding award (and was hence included in the *Guinness Book of World Records*) for being able to sniff subtle chemical changes, and then alerting his type 1 diabetic owner on an ongoing hypoglycemic episode (Figure 1) [6].

Some time ago we published an article aimed at reviewing scientific evidence on the use of DADs for a cost-effective approach of diabetes monitoring, which was almost entirely based on anecdotal evidence, non-human studies or case reports [7]. Some years afterward, a larger number of interesting studies were published, which promoted us to provide a narrative, critical update on this matter.

Published evidence on glycemic alerts

The very first study providing some reliable evidence that dogs may be able to warn their diabetic owners about potentially harmful glycemic states was published by Wells et al., in 2008. The authors enrolled 212 type 1 diabetes owning personal dogs (i.e. untrained to detect blood glucose variations) [8]. Each participant was asked to fill in a specific questionnaire for collecting data on dog response to hypoglycemic episodes. Cumulatively, 65.1% of diabetic subjects indicated that the dogs displayed some behavioral reactions during at least one hypoglycemic event, whilst approximately one third of dogs reacted to the vast majority of episodes. Notably, 33% of responders indicated that their dogs displayed some unusual behavior even before the owner recognized that they were suffering from a hypoglycemic state. The most frequent dogs' alert behaviors were vocalizations (61%), licking (49%), staring intently at owner's face (41.3%), nuzzling (41%) or jumping (30%). This first important evidence lead the way to publication of other ensuing studies, which were more focused on the role of DADs, rather than on "normal" pets, for warning owners on potentially dangerous variations of blood glucose concentration.

Rooney et al. enrolled 17 diabetic subjects (one with type 1 diabetes and the remaining 16 with type 2 diabetes), who had owned a DAD (six Labrador Retrievers, two Labradoodles, two Labrador Retriever/Golden Retriever cross, and one Golden Retriever, one Collie Cross, one Poodle, one Yorkshire Terrier, one Lurcher and one Cocker Spaniel) for a mean period of 1.9 years [9]. Glycemic alerts were identified by blood glucose readings, whilst the exact observation period was not declared (i.e. ≥1 month). Notably, the sensitivity of DADs for alarming their owners to glucose measurements lying outside the target range was 0.80 (95% confidence interval [95% CI], 0.44–0.97), whilst data on specificity were unavailable in this study. Interestingly, glycated hemoglobin (HbA_{1c}) values displayed a modest and non-significant reduction after owning the dog (i.e. 62.7 vs. 61.2 mmol/mol), whilst the rate of blood glucose readings below the target range was remarkably lower after owing DADs (odds ratio [OR], 0.24; 95% CI, 0.17–0.35). Finally, 75% of patients declared that they felt more independent after living with the DAD.

Dehlinger et al. carried out another original investigation using three DADs, which were trained to identify hypoglycemia from a series of sterile cotton swabs rubbed on the skin of three type 1 diabetic patients collected over a spectrum of 24 various glycemic states (half of which were hypoglycemic) [10]. The cumulative diagnostic accuracy, sensitivity and specificity of the three DADs for identifying hypoglycemic samples were 0.55, 0.56 and 0.54, respectively.

In an ensuing study, Hardin et al. assessed the ability of six, 6-month trained DADs (two Labrador Retrievers and one Flat Coated Retriever, one German Shepherd, one Siberian Husky mix and one Spaniel mix) for detecting hypoglycemia in human perspiration samples [11]. Dogs were specifically trained to signal hypoglycemic samples by sitting in front of, or pushing the can containing the sample (the dogs were challenged with seven human perspiration samples, one of which was collected during a hypoglycemic state). The cumulative diagnostic accuracy, sensitivity and specificity of DADs for detecting perspiration samples collected during hypoglycemic episodes were 0.93, 0.78 and 0.96, respectively.

Los et al. performed an exploratory study, including eight subjects with type 1 diabetes, owning a DAD (five Labrador or Labrador mix and one Golden Doodle, one Border Collie and one Saint Bernard) [12]. Glycemic alerts were identified by using continuous glucose monitoring, during a 3-month period. The cumulative sensitivity of DADs for detecting hypoglycemia was 0.36, whilst no information was reported about the specificity (the false positive rate was 14.5). Notably, the combination of DAD alert and onset of subjective symptoms increased by nearly five-fold the chance of being warned about hypoglycemic episodes compared to the presence of subjective symptoms alone (i.e. 62% vs. 12%). Nevertheless, it was also shown that continuous glucose monitoring would have warned the owner prior to the DAD in 73% of cases. Interestingly, the median cost of adopting a DAD was estimated to be between 5000 and 15,000 US $, whilst the home-based training program cost 2000 US $.

Gonder-Frederick et al. carried out another study including 14 diabetics (seven adults with type 1 diabetes and seven youth with type 1 diabetes) who had DADs (all Labrador Retrievers) placed in their home for a minimum of 6 months [13]. Glycemic alerts were identified by using continuous glucose monitoring devices. Overall, 2278 hypoglycemic or hyperglycemic events could be recorded over a median period of 29 days. The DADs cumulative sensitivity and specificity were 0.29 (0.36 for hypoglycemia and 0.26 for hyperglycemia, respectively) and 0.66, thus yielding to a cumulative diagnostic accuracy of 0.48. The accuracy of DADs was characterized by a high inter-dog variability.

Short afterwards, the same team of authors performed another study based on 18 type 1 diabetic subjects who had most DADs (all Labrador Retrievers) in their home for ~3 months [14]. Glycemic alerts were identified by using glucose monitoring devices. Overall, 3006 hypoglycemic or hyperglycemic events could be recorded over a median period of 134 days. The DADs cumulative sensitivity and specificity were 0.57 (0.59 for hypoglycemia and 0.56 for hyperglycemia, respectively) and 0.49, thus yielding to a cumulative diagnostic accuracy of 0.54. Even in this study a highly variable inter-DAD accuracy was observed.

Taken together, the available published studies analyzing dog's efficiency for alerting their owners on episodes of hypoglycemia or hyperglycemia seems hence rather heterogeneous, with sensitivities and specificities ranging between 0.29–0.80 and 0.49–0.96, respectively (Table 1). Moreover, a substantial inter-dog variability has been observed in the majority of the studies.

Additional evidence on glycemic control and quality of life

Gonder-Frederick et al. carried out a small exploratory survey, which was completed by 36 DAD owners (i.e. 13 adults with type 1 diabetes and 23 relatives of children with

Table 1: Summary of human studies analyzing dog's efficiency for alerting the owner on episodes of hypoglycemia or hyperglycemia.

Study	Sample size	Observation period	Outcome	Performance
Rooney et al., 2013 [9]	17 Subjects (1 type and 16 type 2 diabetes)	≥1 Month	Detecting hyperglycemia	0.80 Sensitivity
Dehlinger et al., 2013 [10]	3 Dogs each challenged with 24 Human cotton swabs (12 collected during hypoglycemia)	–	Detecting hypoglycemia	Accuracy, 0.55 (0.56 sensitivity and 0.54 specificity)
Hardin et al., 2015 [11]	6 Dogs each challenged with 7 Human perspiration samples (1 collected during hypoglycemia)	–	Detecting hypoglycemia	Accuracy, 0.93 (0.78 sensitivity and 0.96 specificity)
Los et al., 2017 [12]	8 Type 1 diabetics	3 Months	Detecting hypoglycemia	Sensitivity, 0.36
Gonder-Frederick et al., 2017 [13]	14 Subjects (7 with type 1 and 7 With type 2 diabetes)	Median, 29 Days	Detecting both hypo- and hyperglycemia	Cumulative accuracy, 0.48 (0.29 sensitivity and 0.66 specificity)
Gonder-Frederick et al., 2017 [14]	18 Type 1 diabetics	Median, 134 Days	Detecting both hypo- and hyperglycemia	Cumulative accuracy, 0.54 (0.57 sensitivity and 0.49 specificity)

type 1 diabetes), aimed at identifying glycemic control and quality of life improvements after owing the dog [15]. Overall, a significantly lower rate of severe (no frequency reported; $p = 0.039$) and moderate (no frequency reported; $p = 0.02$) hypoglycemic episodes was declared by responders after owing a DAD, whilst the HbA_{1c} values were also found to be lower after DAD placement (no values reported; $p < 0.001$).

Petry et al. surveyed 135 subjects (72 diabetic patients and 63 parents of children with diabetes) with the aim of evaluating owners' perceptions about DADs (nearly half were Labrador Retrievers) or their DAD's capacity of detecting potentially harmful glucose levels [16]. More than half of responders stated that the dog was capable of frequently identifying (i.e. more than three times per week) low glucose values when the owner was unaware of them, whilst ~80% of responders felt that the dog may have saved his/her life at least once. Finally, the vast majority of responders stated that the dog was very or extremely useful for managing diabetes. According to the replies to this survey, DAD also had a substantial favorable impact on perceived quality of life, by reducing the frequency of hospitalization, need of assistance from other persons, as well as by decreasing the alleged risk of accidents while driving a car.

Lundqvist et al. carried out another longitudinal interventional study including 55 owner-and-dog pairs, 20 of which were DADs [17]. A specific questionnaire aimed at recording several health-related quality of life and activities was administered before and 3 months after adopting the dog. Notably, diabetic owners of DADs reported a higher health-related quality of life compared to that of the general population, but no significant improvement could be recorded after living with the dog. The analysis of the entire study population also revealed that physical activity level, health-related quality of life and well-being had all improved significantly after owing the dog.

What are diabetes alert dogs really perceiving?

Unlike other human diseases, it is likely that dogs may be able to perceive human glycemic variations not only using their exceptional olfactory apparatus, but also by integrating perceptions coming from other senses, mainly from their sight.

Indeed, the canine olfactory apparatus plays a pivotal role for identifying several organic compounds (i.e. the so-called "volatilome") generated during diseased conditions (especially cancer, seizures, infectious and psychiatric diseases), as earlier proven in many published studies [18, 19]. With the aim of replicating dogs' detection ability, Siegel et al. carried out an interesting study, in which VOCs collected from the breath of 52 type 1 diabetics were analyzed with gas chromatography/mass spectrometry (GC/MS) [20]. The ensuing linear discriminant analysis showed that hypoglycemic episodes were associated with highly characteristic signatures, displaying 0.91 sensitivity and 0.84 specificity. In another recent study, Saidi et al. collected breath samples from six diabetic patients, and compared their profiles with those of non-diabetic subjects, using a GC/MS technique [21]. The resulting radar plots were clearly different in diabetics, displaying increased concentrations of benzaldehyde, toluene, methane, aniline and carbonochloridic acid. Other studies were capable of identifying a number of putative VOCs in the exhaled breath during hypoglycemia, which may then be sniffed by dogs. These basically include isoprene [22], along with a vast array of volatile substances that are typically increased during hypoglycemia such as ketones (e.g. acetone and acetaldehyde), hydrocarbons (e.g. ethane, pentane and isoprene), acetaldehyde, methanol and ethanol [23]. This preliminary evidence leads the way for planning further investigation aimed at exploring the association between dogs' alerts and variation of measured volatile organic in exhaled breath or in other biological fluids (e.g. sweat or saliva) during hypoglycemic episodes and, especially, in the context of severe hyperglycemia, for which no reliable studies have been published so far [24].

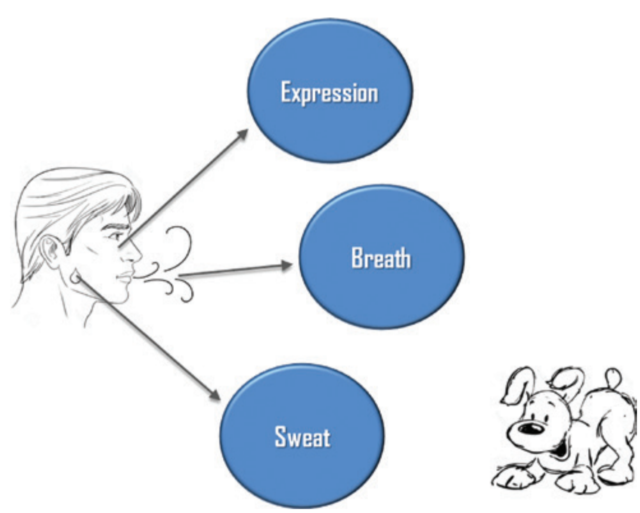

Figure 2: A dog's cognitive apparatus may be able to elaborate and integrate a number of different owner's olfactory and visual signals, which may finally help recognizing harmful clinical conditions.

It is now unquestionable that dogs can read human facial expressions and postures. In particular, recent studies showed that dogs are very sensitive to emotional expressions conveyed by the human face [25], emotional vocalizations [26] and sudden change of attention or posture [27], thus being even able to discriminate between positive and negative emotions [28]. It is hence conceivable that the dog's cognitive apparatus may be able to elaborate and integrate a number of different owners' olfactory and visual signals, which may finally help the pet recognizing harmful clinical conditions (Figure 2).

Discussion

Although most of us would agree that DADs have a conjectural potential for improving the quality of life (both clinical and social) of many diabetic patients (Table 1), at least those who are not allergic and can love and respect them, some important drawbacks can be easily identified for using these pets as diagnostic aids (Table 2).

The first issue relates to the cost for adopting and keeping these "special" dogs. The current expenditure of a DAD varies widely, from approximately one to several thousands of US $. For example, an US organization applies an one-time fee of 1600 US $ for providing a completely trained DAD [29], whilst others have prices ranging from 8500 US $ [30] to over 20,000 US $ [31], or target the cost depending on individual needs [32]. Occasionally, DADs may also be provided by not-for-profit organizations, but these are only sporadic cases in the growing DAD industry. No country has made the adoption of DADs refundable so far, and hence purchasing and keeping the pet may pose a considerable economic burden on some diabetic subjects and their families. Then, no official certification or accreditation exists for associations, organizations or even single trainers of DADs, so that it cannot be taken for granted that dogs have been appropriately or accurately trained to detect severe blood glucose fluctuations.

Table 2: Current drawbacks of diabetes alert dogs.

- Cost for adopting and keeping the dog
- Certification or accreditation of dogs' providers
- Harmonization of training procedures
- Inter-breed, intra-breed and intra-dog variability
- Heterogeneity of dogs' alert behaviors
- Capability of owners to identify altered behaviors
- Quality assurance and verification
- Quality indicators

As a mainstay of diagnostic testing, the "calibration" procedure is critical for obtaining accurate and, especially, comparable clinical information across different settings [33]. Albeit the DAD's training procedures used in the different studies were mostly based on positive reinforcement and standard training stimuli (e.g. usually with food), thus avoiding coercion-based strategies, each trainer exploits a specific method and, understandably, dogs are not laboratory instrumentation, so that they will manifest a highly subjective reaction to training and stimuli. Therefore, although standardizing training procedures seems a reachable goal, harmonization of individual dog's behaviors will probably remain an unmet target [34].

A large inter-breed, intra-breed and even intra-dog variability of olfactory capacity has been clearly described. Irrespective of the huge heterogeneity in the total number of olfactory receptors across different breeds, ranging between 120 million in Dachshunds to over 300 million in Bloodhounds [35], Tacher et al. analyzed the sequence of as many as 16 olfactory receptor genes in 95 dogs of 20 different breeds [36], and found high molecular heterogeneity, leading to significant amino acid variations. This perhaps contributes to justify the different odor discrimination performance observed across different breeds (e.g. wolves and scent dogs such as German Pointers, Basset Hounds and Beagles, perform much better than short-nosed dogs or non-scent breeds), as well as among dogs belonging to the same breed [37]. These findings were then replicated by Lesniak et al., who also found that some polymorphisms in certain genes may have a considerable impact on canine odor sensing skills [38, 39]. Importantly, circadian and locomotors behaviors [40], along with metabolic variations [41], also induce significant variations of olfactory perceptions. It is hence predictable that the individual odor discrimination performance of dogs might display a substantial within-day and day-to-day variability.

The heterogeneity of dogs' alert behaviors, as well as the capability of a dog's owner to identify altered behaviors, are additional limitations. The current published studies have listed a large number of potential alert behaviors, including barking, whining, hiccupping, licking, yawning, scratching, biting, nudging, nuzzling, jumping or staring intently at the owner's face [8, 9]. All these are commonplace dog activities, and it will not be easy for the owner to distinguish whether an unusual behavior of his/her dog has been triggered by severe glycemic derangements or by another environmental circumstance. Then, even the owners themselves may not have enough skill, vigilance or be ready to capture these alert behaviors, so that there is a tangible risk that dog's warning may go overlooked.

From a genuine technical perspective, to which we are especially attached as we are both clinical biochemists, quality assessment of dogs' olfactory performance is still an unexplored domain. Quality assurance and verification [42, 43], along with regular use of quality indicators [44], are now essential parts of total quality in laboratory diagnostics. Albeit the translation of these concepts to dogs' olfactory performance seems not easy and straightforward, because the "quality control material" cannot be different from the owners themselves (e.g. each human has a virtually unique smell fingerprint, to which the pet is accustomed) [45], poor individual performance of the dog, or progressive decay of odor sensing skill over time, may then generate an unacceptable rate of false negative and false positive alerts, which may either falsely reassure the owner about a normal (i.e. euglycemic) state or generate unnecessary and unjustified concern, respectively. It may hence be necessary to define standard operating procedures to be used by owners for continuous monitoring of their dog's alert performance, more or less like routine checking the accuracy of glucose meters or continuous glucose monitoring devices. A simple approach may be based on the use a diary for correlating glucose fluctuations with dog's behaviors, especially focused on registering episodes of hypoglycemia and hyperglycemia. The owner's personal physician (or diabetologist) may then calculate and number of false positive and false negative alerts, benchmarking them with their dog's previous accomplishments or with other DADs' performance. Nevertheless, like other diagnostic domains, this second aspect shall first need to develope reliable quality indicators [46] and informatics tools, where a dog's olfactory performance could be recorded in a consistent and standardized manner, and then be compared with benchmark performances [47].

Conclusions

In conclusion, the current published evidence attests that DADs may contribute to provide some undeniable health [48] and psychological [49] benefits to diabetic people, though their efficiency for detecting harmful, even life-threatening, blood glucose variations remains questionable. Some important case reports have demonstrated that "man's best friends" have actually saved the lives of some diabetic subjects, especially when immediate glucose monitoring was unavailable [7]. Therefore, it is the authors' opinion that albeit DADs will never replace self-testing, especially glucose continuous monitoring, their gracious and affectionate presence may still be a valuable aid for promoting healthier lifestyles, for improving the overall quality of life in diabetes and, under special circumstances, for warning owners on dangerous glucose fluctuations.

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