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Dosing obese cats based on body weight spuriously affects some measures of glucose tolerance

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ABSTRACT

The primary objective was to investigate whether dosing glucose by body weight results in spurious effects on measures of glucose tolerance in obese cats because volume of distribution does not increase linearly with body weight. Healthy research cats (n = 16; 6 castrated males, 10 spayed females) were used. A retrospective study was performed using glucose concentration data from glucose tolerance and insulin sensitivity tests before and after cats were fed ad libitum for 9 to 12 mo to promote weight gain. The higher dose of glucose (0.5 vs 0.3 g/kg body weight) in the glucose tolerance tests increased 2-min glucose concentrations ($P < 0.001$), and there was a positive correlation between 2-min and 2-h glucose ($r = 0.65$, $P = 0.006$). Two-min ($P = 0.016$ and 0.019, respectively), and 2-h ($P = 0.057$ and 0.003, respectively) glucose concentrations, and glucose half-life ($T_{1/2}$; $P = 0.034$ and <0.001 respectively) were positively associated with body weight and body condition score. Glucose dose should be decreased by 0.05 g for every kg above ideal body weight. Alternatively, for every unit of body condition score above 5 on a 9-point scale, observed 2-h glucose concentration should be adjusted down by 0.1 mmol/L. Dosing glucose based on body weight spuriously increases glucose concentrations at 2 h in obese cats and could lead to cats being incorrectly classified as having impaired glucose tolerance. This has important implications for clinical studies assessing the effect of interventions on glucose tolerance when lean and obese cats are compared.

1. Introduction

The intravenous glucose tolerance test (GTT) was introduced in human medicine in 1923 to assess glucose homeostasis [1] and measures an individual's ability to clear glucose from circulation after a bolus dose of glucose. People with impaired glucose tolerance are considered prediabetic and at high risk of developing type 2 diabetes [2–4]. Measures of glucose tolerance include glucose half-life ($T_{1/2}$) and rate of glucose clearance (Kglucose), but these require multiple blood samples and complex mathematical calculations. In clinical practice, blood glucose concentration 2 h after a standardized oral glucose dose (75 g/adult person) is currently used to identify humans with impaired glucose tolerance [5,6].

Approximately, 1 in 200 to 400 domestic cats and 1 in 50 Burmese cats of European origin develop diabetes analogous to human type 2 diabetes [6–10]. As in humans, if diagnosed in the prediabetic state, clinical disease can likely be averted or minimized through diet and weight loss [11]. However, tests for prediabetes are not well characterized or commonly used in clinical veterinary practice,

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and cats are usually not diagnosed until overt diabetes is evident [8].

A number of criteria for classification of glucose tolerance in cats have been published [9,10,12]. The "gold standard" test is tedious, requires multiple blood samples, and interpretation can be difficult because of the complex calculations required, such as glucose half-life, rate of glucose clearance, and area under the curve [7,13]. For many cat owners, the procedure is unacceptably expensive and invasive. A routine screening test equivalent to the test in human medicine, based on absolute glucose concentrations and requiring 2 blood samples, was reported in 1998 but has not been widely implemented for cats [7]. Although there are inherent problems associated with interpreting absolute glucose values [14], these measures form the basis of a satisfactory primary screening test for prediabetes in humans [3] and could be similarly used for cats.

In humans, oral administration of glucose has replaced intravenous administration, due to its ease and practicality [3]. Oral glucose administration has been reported in cats and, as in humans, results in greater insulin stimulation through an incretin effect [15]. However, cats are very susceptible to stress hyperglycemia and may be stressed by oral administration which would confound the assessment of glucose tolerance [16]. Stress, particularly if it results in struggling, can increase blood glucose concentrations by as much as 10 mmol/L and take 3 h to resolve [16], and therefore needs to be avoided. Placing a cephalic catheter for glucose injection 3 h before the test starts likely assists in preventing struggling and stress-induced hyperglycemia during the test.

A recent study in dogs reported a spurious effect on evaluation of glucose tolerance when glucose was dosed on a body weight basis in obese dogs, resulting in higher peak glucose concentrations and higher area under the glucose curve, incorrectly implying impaired glucose tolerance [17]. For the analysis of glucose tolerance, this was resolved by adjusting the measured glucose concentrations, based on peak glucose concentration. The observation that peak glucose concentration was higher in obese dogs compared with lean dogs when dosing glucose based on body weight is not surprising. For a substance injected intravenously, the volume of distribution (and circulating blood volume), expressed as a percentage of body weight, is reduced in obese individuals because it does not increase linearly with increasing fat mass [17–19]. Therefore, when administering glucose at a dose based on body weight, obese cats are potentially overdosed in comparison with cats in ideal body condition, which could lead to a false assessment of impaired glucose tolerance. No studies investigating clearance of anesthetic agents or sedatives or allometric scaling in cats have been identified [20].

The purpose of this study was to investigate effects of changes induced by obesity on absolute glucose concentrations measured at various times after a bolus dose of intravenous glucose. We then determined the effect of these obesity-induced changes on assessment of glucose homeostasis, in particular, diagnosis of glucose intolerance and investigated whether the adjustment for glucose dose was indicated in obese cats. Such information is important for the development of reference values for a simple clinical test for glucose intolerance in cats that requires only a fasting and a 2-h blood sample.

2. Materials and methods

A retrospective study was conducted using data from a previous study that investigated the effect of obesity on various glucose variables. That study was approved by the Animal Experimentation and Ethics Committee of the University of Queensland. In the present study, we examined the effects of body weight and body condition on variables including peak and 2-min glucose after glucose administration, fasting glucose, glucose dose (0.3 and 0.5 g/kg), and measures of glucose tolerance such as $T_{1/2}$ and 2-h glucose concentration. We used blood glucose concentration data from GTTs and the first 2 min from insulin sensitivity test previously performed at our laboratory on 16 cats before and after weight gain [13,21]. In the original study, 16 (10 spayed females, 6 castrated males) clinically healthy research cats between 1 and 5 yr of age (most in ideal body condition) underwent glucose tolerance and insulin sensitivity tests to provide baseline data before weight gain [21]. The cats were offered a combination of 2 commercially available extruded foods, with metabolizable energy consisting of 33% protein, 22.3% fat, 30.2% carbohydrate and 40% protein, 26.6% fat, and 17.2% carbohydrate, respectively [21]. The tests were repeated after a weight gain period, when cats were fed ad libitum for an average (±standard deviation [SD]) of 10.5 (±1.1 mo; range, 9–12 mo) [22]. Based on dual energy, x-ray absorptiometry, after the weight gain period, all cats had more than 30% body fat (range 34.2%–48.7%) [21].

Body condition score (BCS) was originally measured on a 5-point scale [23]. For the present study, these scores were converted to a 9-point scoring system, where scores of 1, 2, 3, 4, and 5 on the 5-point scale were converted to 1, 3, 5, 7, and 9, respectively, on the 9-point scale to allow better comparison with other data sets [24]. All BCSs were measured by the same person.

In the original study, glucose tolerance and insulin sensitivity tests were performed on separate days [13]. For the GTT, glucose was administered at 0.5 g/kg as a bolus dose over 30 s, via a jugular vein catheter. Blood samples were collected before glucose administration (4 samples at −15, −10, −5, and −1 min) and after (at 2, 5, 10, 15, 30, 45, 60, 90, and 120 min). For the insulin sensitivity test, glucose was administered at 0.3 g/kg as a bolus dose over 30 s, via a jugular vein catheter, and insulin was injected 20 min later. Glucose concentration data before and 2 min after glucose injection in the insulin sensitivity test was used to compare the effect of glucose dose on 2-min blood glucose concentration after injection of 0.3 g/kg glucose and 0.5 g/kg from GTT. Data from blood samples collected after insulin administration could not be used due to effects of insulin on glucose concentrations, precluding the calculation of $T_{1/2}$, and time to return to baseline for the 0.3 g/kg dose rate. In both tests, the timer was started halfway through infusion. Glucose was measured in plasma using an automated glucose analyzer which had a precision for replicate analyses of <2% (YSI 2300 Stat Plus; Yellow Springs Instrument Co) [13].