Case Report

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Fasting blood glucose and hemoglobin a1c: measures of insulin sensitivity?

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INTRODUCTION

Measures used in clinical practice should be indicative of health or disease. Fasting blood glucose and hemoglobin a1c are used routinely in clinical practice to diagnose diabetes but the utility of fasting blood glucose and hemoglobin a1c as measures of tissue sensitivity to insulin is unreliable at best. It has been observed in a number of studies (Table 1.), that fasting blood glucose does not change substantially in response to interventions that substantially change tissue glucose uptake or in other words insulin sensitivity. Kirwan et al. [1] published a representative study where large improvements in glucose disposal were not associated with improvements in fasting glucose. Specifically, insulin-stimulated glucose disposal, during the first stage of a euglycemic-hyperinsulinemic clamp, was improve 45.1% after 7 days of exercise (60 min per day). However, fasting blood glucose was relatively unchanged (-5.1%). As shown in several similar studies presented in Table 1 this appears to be "the rule" not an "exception". With a small change of -5.1% (compared to 45.1% with the euglycemic-hyperinsulinemic clamp) this measure, fasting blood glucose, is not precise enough to detect differences in the fasting blood glucose with exercise training.

What then does fasting glucose reflect?

Homeostasis is a rudimentary physiological principle. Because fasting glucose levels do not change substantially in response to stimuli that induce substantial changes in gold standard measures of insulin sensitivity, it may not provide an adequate reflection of patient status. Instead the fasting glucose is likely reflective of the body's attempt to maintain homeostasis. Despite the lack of change in fasting glucose with exercise training, the capacity to correct drastic changes in blood glucose concentrations is altered dramatically. For example, liver glycogen is depleted by a 24-hour fast [2] but blood glucose is not altered substantially.[3] It is well documented that hepatic glycogenolysis is the primary mechanism by which glucose is released into the blood during fasting or exertion. Thus, alternatively, elevated fasting glucose may be reflective of a homeostatic mechanism to prevent hypoglycemia.

HEMOGLOBIN A1C

Changes in Hemoglobin A1C are not reflective of changes in insulin resistance or insulin sensitivity

Perusal of Table 2. Using changes in insulin sensitivity from similar studies in Table 1. Infers that hemoglobin A1C is unresponsive to changes in insulin sensitivity. Chronic exercise training does not seem to measurably change hemoglobin A1C levels but from Table 1 changes insulin sensitivity using better measures of insulin sensitivity show robust changes. It is clear that chronic exercise will change insulin sensitivity as measured by more sensitive methods but hemoglobin A1C is very unresponsive to these interventions; suggesting a problem with the method.

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Table 1. Representative publications illustrating the disparity between changes in glucose disposal and fasting glucose, after an exercise intervention

Authors	Intervention	% Improvement in IS	* % Decrease in FG
Kirwan et al. [1]	7 days of exercise training (60 min)	45	5
Ferrara et al. [4]	6 months of exercise training (3 days/week)	23	1.7
Gillen et al. [5]	3 months of interval training (3 days/week)	53	-8
Wang et al. [6]	1 bout of 1 hour of walking	10.9	3.4
Arciero et al. [7]	10 days of exercise training (60 min)	56	9.8
Weiss et al.	12 months of exercise	67 (as measured by insulin sensitivity index from an oral glucose tolerance test)	1.5 (non-significant p=0.06)

IS=glucose disposal from euglycemic-hyperinsulinemic clamp; FG=fasting glucose *%Decrease in FG calculated as (Pre-Post/Pre)X100

Table 2

Authors	Intervention	% improvement in IS	% Decrease in HBA1C*
Church et al.	9 months of exercise training (150 min/wk)	Not measured	No change
Sigal et al.	5.5 months (aerobic, resistance, and combined)	Not measured	5.83 mean change for the 3 groups
Byrkjeland et al.	12 months of exercise training	Not measured	No change
Johansen et al.	12 months of intensive lifestyle intervention	Not measured	4.7 (non-significant p=0.15)
Senechal et al.	9 months of exercise training	Not measured	5.3 combined aerobic and resistance exercise group

*% Decrease calculated as (Pre-Post/Pre) X 100

What are potential clinical ramifications?

One strategy would be that General Practioners use more involved and accurate measures of tissue insulin sensitivity. Naturally, this would require a substantial change in common practice. Another approach, and one that is less reliant on outcomes of measured tissue insulin sensitivity, would be to make sure patients with type II diabetes mellitus were consistently exercising. Exercise (1 hour per day at relatively low intensity (60-65 percent of VO2 max) appears to be extremely effective at improving insulin sensitivity, even after only 1 [6] or 7[1] sessions of exercise. This effect of exercise is relatively short lived (Vukovich).

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