



POSTER NO 12

Glucose vs. Fatty Acid Metabolism in the Human **- A model for Impaired Glucose Metabolism, Type II Diabetes, and Obesity**

The following abstract advances a foundational shift in the rationale for the regulation of lipolysis and glycolysis in the human. Wolfe proposes that it is the availability of glucose or glycogen that controls fatty acid oxidation rather than the reverse hypothesis which had been held for over 35 years. When taken to the next logical step, Wolfe's mechanism or model better explains what happens with impaired glucose metabolism and the resultant development of type II diabetes and obesity. This understanding also underscores the role for honey in driving fat metabolism during rest and combating two key factors in the metabolic syndrome.

Wolfe, RR, "Metabolic interactions between glucose and fatty acids in humans", **American Journal of Clinical Nutrition**, Vol. 67, 519S-526S, © 1998 by The American Society for Clinical Nutrition, Inc.

ABSTRACT

In vivo energy production results largely from the oxidative metabolism of either glucose or fatty acids. Under diverse physiologic and nutritional conditions, the oxidation of either glucose or fatty acids may predominate. The nature of the control of the availability and oxidation of each substrate has been studied extensively for more than 30 years. The most popular and enduring hypothesis was proposed by Randle *et al* in 1963 and is termed the glucose-fatty acid cycle. This proposal places great significance on the regulation of lipolysis as a factor controlling substrate metabolism.

Key Steps:

Our work has led to an opposite perspective, which could be called the glucose-fatty acid cycle reversed. According to our hypothesis, the rate of glycolysis, determined by the intracellular availability of glucose-6-phosphate, is the predominant factor determining the rate of glucose oxidation. Whereas the rate of lipolysis may have some effect on the availability of glucose, both via a fatty acid-mediated inhibition of plasma glucose uptake and also by supplying glycerol for gluconeogenesis, there is little evidence for a direct inhibitory effect of fatty acid oxidation on the intracellular oxidation of glucose. In contrast, increased glucose oxidation limits oxidation of long-chain fatty acids directly by inhibiting their transport into the mitochondria.

Consequently, whereas there is a close coupling between glucose availability and oxidation, fatty acids are generally available in greater quantities than are required for oxidation. We propose that fatty acid oxidation is largely controlled at the site of oxidation, which is in turn determined by the availability of glucose, rather than by its availability via lipolysis.

EDITOR'S COMMENT

This review article, from 1998, is one of the seminal moments in 20th century metabolic science. Wolfe overturned one of the most important and widely held principles of metabolism of that century, the glucose-fatty acid cycle, which originated from Randle in 1963. This cycle was based on the notion that glucose metabolism is controlled by oxidation of fatty acids. Wolfe demonstrated that the opposite is the case and that metabolism of fatty acids is secondary to the metabolism of glucose.

If we factor in to this view the inhibition of glucose disposal by chronic stress which impairs glucose disposal, we have our model for type II diabetes and obesity. Chronic stress inhibits glucose metabolism and glucose disposal in cells. This in turn inhibits fat metabolism and disposal. The result is that both fuels, now considered excess energy intake by the human system, are stored as visceral fat (along with other consequences of the metabolic syndrome). By refueling liver glycogen and by improving glucose metabolism and disposal in peripheral cells, HONEY consumption (compared to other refined sugars) reduces metabolic stress and improves fat metabolism and disposal, thus combating two of the key parameters of metabolic syndrome, type II diabetes and obesity.

A Model for Type II Diabetes and Obesity **Key Steps:**

1. Glucose (glycogen) availability controls fatty acid oxidation (fat metabolism).
2. Chronic adrenal stress produces impaired glucose metabolism
3. Which in turn inhibits fat metabolism and disposal.
4. The result is the *Metabolic Syndrome* or Insulin Resistance with visceral obesity, increased risk of diabetes, CV disease and dyslipidaemia