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Human glycemic response curves after intake of carbohydrate foods are accurately predicted by combining *in vitro* gastrointestinal digestion with *in silico* kinetic modeling

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SUMMARY

Background: Frequent high blood glucose concentrations are associated with increased risks of metabolic diseases. Knowledge about the glycemic response after food intake is essential in relation to human health. The American Association of Cereal Chemists recommends the development of reliable *in vitro* methods for standardized assessment of the human glycemic response after intake of carbohydrates.

Aim: To realize a cost-efficient *in vitro–in silico* technology to predict reliably the human glycemic concentration curve after intake of different carbohydrate products or meals.

Methods: We developed and validated a combined technology based on *in vitro* mastication of foods, digestion of the carbohydrates, availability for absorption of glycemic saccharides, and (based on these *in vitro* data as input) *in silico* prediction of glycemic response curves in humans.

Results: The predicted curves were compared with human clinical data for 22 different food products. The results showed a correlation coefficient for glucose $iAUC_{0-120}$ and glucose C_{max} of 0.89 and

Abbreviations: bw, body weight; C_{max}, maximum concentration (blood glucose); HOMA, homeostatic model assessment (Wallace et al., 2004); $iAUC_{0-120}$, increment of area under (blood glucose) curve from 0 to 120 min; rpm, rounds per minute; TIM, TNO (gastro) Intestinal Model; t_{max}, time at what the maximum concentration has been reached.

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0.94, respectively. Also the shape of the curves and t_{max} were very similar for 18 out of 22 products, while 4 products showed an 'early' *in vitro* t_{max} compared to the human data.

Conclusion: Based on the demonstrated accuracy and predictive quality, this *in vitro–in silico* technology can be used for the testing of food products on their glycemic response under standardized conditions and may stimulate the production of (s)low carbs for the prevention of metabolic diseases.

1. Introduction

The 'glycemic response' is defined by the American Association of Cereal Chemists (AACC) as the change in blood glucose concentration induced by ingested food [1]. The postprandial glycemic response can be used to calculate the glycemic impact, glycemic index, and glycemic load as defined by the AACC [1] and Monro & Shaw [2] to assess whether the intake of a carbohydrate product results in a low or high and in a slow or rapid increase in the blood glucose concentration. This knowledge is important because of the relation between frequent high blood glucose concentrations and the increased risk of diabetes type II, coronary heart disease, gall bladder disease, and colorectal, breast and endometrial cancer as found in literature reviews and meta-analysis studies [3–7].

Blood glucose concentrations are conventionally measured in human volunteers through frequent blood sampling after the ingestion of carbohydrate containing foods [8,9]. The Glycemic Carbohydrate Definition Committee of the AACC has expressed their concern about considerable intra- and inter-individual variability of this *in vivo* measurement [1,10]. Other drawbacks are the ethical constrains of frequent invasive blood sampling and the fact that this method is time consuming as well as expensive. Therefore the AACC committee recommends the development of new effective *in vitro* methods. Although several *in vitro* methods had been reported, they differ considerably in terms of physiological relevance and assessment of the glycemic potency of food products [11]. This diversity of methods is due to oversimplification of the physiological conditions in the gastrointestinal tract and adaptations of the method to fit the test product. To overcome this, a general method should be designed that can handle realistic types of foods and simulates all relevant digestion parameters, such as particle sizes, mixing with digestive enzymes, gastric and intestinal pH values, gastric emptying times, insulin response and clearance. Only in this way it is possible to test a wide range of products and meals with a reliable prediction of the glycemic response in humans.

We describe the *in vitro–in vivo* validation of a novel *in vitro–in silico* technology (TIMcarbo) that accurately measures the digestibility of foods, the availability for absorption of glycemic carbohydrates and reliably predicts the human glycemic response in a standardized and time- and cost-efficient way without ethical constraints.

2. Materials and methods

2.1. Overview of the TIMcarbo technology

The TIMcarbo technology consists of four successive steps to follow the physiologically relevant events that determine the blood glucose curve after intake of a meal (Fig. 1). After artificial mastication of the food, the carbohydrates were digested to di- and oligosaccharides in a dynamic *in vitro* model simulating the passage of food through the lumen of the upper gastrointestinal tract. The small saccharides were dialyzed from the lumen. The dialysate was collected in 10-min aliquots and further digested by a mixture of enzymes as produced by the intestinal mucosal cells, the brush border

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