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Relationship between whole-body macronutrient oxidative partitioning and pancreatic insulin secretion/ β -cell function in non-diabetic humans

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Abstract

Background—Glucose-stimulated insulin secretion correlates inversely with the degree of whole-body insulin sensitivity suggesting a crosstalk between peripheral organs and pancreas. Such sensing mechanism could be mediated by changes in glucose flux (uptake, oxidation or storage) in peripheral tissues that may drive insulin secretion.

Aim—To relate whole-body non-protein respiratory quotient (npRQ), an index of macronutrient oxidative partitioning, with insulin secretion and β -cell function in non-diabetic individuals.

Methods—Macronutrient oxidation was measured after an overnight fast and for 4 hours after a 75-g oral glucose tolerance test (OGTT) in 30 participants (15/15 males/females; 35 ± 12 y; 27 ± 4 kg/m²). Furthermore, npRQ was assessed for 24 hours in a metabolic chamber. Insulin secretion was estimated by deconvolution of serum C-peptide concentration (fasting and 4-h OGTT) and from 24-h urinary C-peptide excretion corrected for energy intake (metabolic chamber). β -cell function parameters were obtained by mathematical modelling, while insulin sensitivity was determined by a euglycemic-hyperinsulinemic clamp ($120 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}$).

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

JEG designed the study, analyzed and interpreted the data, and drafted/revised and approved the final version of the manuscript. MLM interpreted the data, drafted/revised and approved the final version of the manuscript. AM analyzed insulin secretory rate, interpreted the data, revised and approved the final version of the manuscript. ER interpreted the data, revised and approved the final version of the manuscript.

Results—Insulin secretion (from 24-h urinary C-peptide) correlated inversely with 24-h npRQ ($r=-0.61$; $p=0.001$), even after controlling for insulin sensitivity, energy balance, age and body mass index ($r=-0.52$; $p=0.01$). In turn, insulin secretion (from serum C-peptide) was not associated with fasting or OGTT npRQ. However, fasting npRQ was positively correlated with rate sensitivity ($r=0.40$; $p<0.05$) and marginally with glucose sensitivity ($r=0.34$; $p=0.08$).

Conclusion—Macronutrient oxidative partitioning, specifically glucose oxidation, might play a role on the regulation of insulin secretion. Further studies should aim at identifying the signals linking these processes.

Keywords

Skeletal muscle; Insulin resistance; Respiratory quotient; Glucose flux

1. Introduction

Systemic glucose homeostasis is a complex process in which pancreatic β cells sense glucose flux and release insulin to keep glycemia within a narrow range. Optimal insulin secretion must be adjusted to insulin demand, so hypo- or hyper-glycemia is prevented [1]. In this scenario, an inverse relationship between insulin sensitivity and insulin secretion is commonly observed [2]. Therefore, the amount of secreted insulin in response to glucose stimulation has to be gauged in the context of the degree of insulin sensitivity. Such regulation suggests the existence of a crosstalk between the pancreas and the insulin-target tissues [3].

A major insulin-target tissue is skeletal muscle, which is a main site of insulin-stimulated glucose disposal [4] and also the largest tissue in non-obese subjects [5]. Then, skeletal muscle may be part of such organ crosstalk between insulin-sensitive tissues and the pancreas. In this regard, skeletal muscle mitochondrial disturbances due to a gene-targeted modification proved to impair *in vivo* insulin secretion in a mice model [6]. In turn, blocking IL6 (a main skeletal muscle- and adipose tissue-derived cytokine) action resulted in impaired insulin secretion with simultaneous deterioration of glucose tolerance in *db/db* mice [7].

In humans, the infusion of glucose for 80 min following a 4-h isoglycemic-hyperinsulinemic clamp vs. 4-h saline infusion, increased insulin secretion in healthy individuals [8, 9]. Such finding has been considered as a proof of the insulin-enhancing effect on its own secretion [8, 9]. Alternatively, it may also be interpreted under the context of an inter-organ crosstalk, on which the increase in insulin-stimulated glucose flux in peripheral tissues, particularly skeletal muscle, may drive insulin secretion.

We here hypothesize that whole-body fuel oxidative partitioning is part of the sensing mechanism driving insulin secretion. By using data from a study designed to assess concordance between surrogate markers of insulin sensitivity [10], we searched the association between whole-body non-protein respiratory quotient (npRQ), an index of macronutrient oxidative partitioning, with insulin secretion and β -cell function in non-diabetic individuals.

2. Methods

2.1 Subjects

Thirty healthy (physical examination and routine laboratory tests), non-smoking, non-diabetic participants (15 males and 15 females) were recruited by advertising [10]. They all had a stable body weight (change <2 kg) over the past 3 months and none performed regular physical activity (<60 min/week) or took medications (Table 1). The protocol was approved by the Pennington Biomedical Research Center Institutional Review Board, and all participants provided written informed consent. Body fat mass was measured on a Hologic dual-energy x-ray absorptiometer in the fan beam mode (QDR 4500; Hologic, Waltham, MA, USA). Fat-free mass (FFM) was calculated as the difference between body mass and fat mass.

2.2 Experimental design

Participants were instructed to avoid vigorous physical activity for the two days preceding metabolic testing. One day before metabolic testing, subjects were admitted at the Pennington Center in-patient unit for a 3-day stay period. Participants were fed with a standardized eucaloric diet (50% carbohydrate, 20% protein, and 30% fat). Following a 12-h overnight fast, a 75-g oral glucose tolerance test (OGTT) was performed. Blood samples were collected over 4 hours for analysis of glucose, insulin and C-peptide concentrations. Gas exchange was measured using a Deltatrac II metabolic cart (Datex-Ohmeda, Helsinki, Finland) for 30 min before and during the last 20 min of each hour after glucose ingestion. The analyzers were calibrated before each study with standardized gases containing 5% CO₂ and 95% O₂. A transparent plastic hood connected to the device was placed over the head of the participant. VO₂ and VCO₂ were calculated at 1 min intervals from continuous measurements of CO₂ and O₂ concentrations. Energy expenditure was calculated after standardization for temperature, pressure and moisture. Energy substrate oxidation was calculated taking into account urinary nitrogen excretion rate [11]. The experimental design is depicted in Figure 1.

2.3 Metabolic chamber

The next morning, subjects entered the respiratory chamber at 8:00 AM for assessment of 24-h energy expenditure. Total urine was collected for measurements of nitrogen and C-peptide excretion. Daily energy expenditure and fuel oxidation were measured at energy balance using an algorithm to balance intake and expenditure within the day [12]. No exercise was allowed in the chamber. The diet (50% carbohydrates, 30% fat, and 20% protein with a food quotient of 0.88) was standardized for energy supply, type of food, meal preparation, and served according to a fixed schedule. Breakfast, lunch, and supper provided 25, 35 and 40% of the total energy, respectively. Participants were instructed to eat all foods provided. Carbohydrate oxidation and its balance were expressed per kg of estimated metabolic body size (EMBS = FFM [kg] + 17.7) [13].

2.4 Euglycemic–hyperinsulinemic clamp

After leaving the respiratory chamber at 7.15 AM, participants were set up for a one-step euglycemic-hyperinsulinemic clamp. Insulin ($120 \text{ mU}\cdot\text{m}^{-2}$ per min) was infused for two hours, while a 20% glucose solution was infused to maintain glycemia at $90 \text{ mg}\cdot\text{dl}^{-1}$ [14]. Serum insulin concentration was measured at 10 min intervals at baseline and during steady-state from 90 to 120 min. The glucose disposal rate was expressed in $\text{mg}\cdot\text{min}^{-1}$ per kg of EMBS.

2.5 Insulin secretion rate from C-peptide analysis

2.5.1 Serum C-peptide concentration—Insulin secretory rate during the 4-h OGTT was calculated by deconvolution of the plasma C-peptide concentration curve. β -cell function parameters were obtained using the model by Mari et al. [15, 16]. This model expresses glucose-stimulated insulin secretion (in $\text{pmol}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$) as the sum of two components. The first component represents the dependence of insulin secretion on the absolute glucose concentration at any time point during the OGTT and is characterized by a dose-response function relating the two variables. A characteristic parameter of the dose-response is its slope, denoted as β -cell glucose sensitivity. The dose-response is modulated by a *potentiation factor* that encompasses several glucose-dependent and glucose-independent potentiating mechanisms (e.g., prolonged exposure to hyperglycemia, non-glucose substrates, gastrointestinal hormones, neural modulation, and molecular/biochemical/enzymatic changes within the β cell). In normal individuals, the potentiation factor typically increases from baseline to the end of the OGTT; this increase is quantified by the ratio of 120 min post OGTT and baseline (potentiation factor ratio [PFR]). The *second secretion component* represents the dependence of insulin secretion on the rate of change of plasma glucose concentration and is proportional to the first derivative of plasma glucose concentration against time; the proportionality parameter is denoted as *rate sensitivity*. Rate sensitivity accounts for the observation that rapid changes in glucose concentration enhance insulin secretion early in the OGTT.

2.5.2 Urinary C-peptide excretion—Insulin secretion was estimated from C-peptide urinary excretion collected over 24 hours during the chamber stay. Considering that insulin secretion (and so, C-peptide secretion) relates with the amount of carbohydrates ingested and actual energy needs [10], C-peptide excretion was divided by total energy intake. Thus, 24-h insulin secretion rate was expressed in μg of C-peptide excreted per kcal of ingested energy.

2.6 Blood and urine analysis

Serum glucose concentration was measured by the glucose oxidase method on a Beckman Coulter DXC 600 Pro. Insulin and C-peptide concentrations were analyzed using immunoassays on a Siemen's Immulite 2000 instrument.

2.7 Statistical analysis

Data are presented as means $\pm$ SD. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Associations between variables were analyzed by Spearman rank

correlations, and as needed, controlled for confounding variables using PARTIAL function. $p < 0.05$ was considered significant.

3. Results

3.1 Fuel oxidation and insulin sensitivity

Total energy expenditure measured in the metabolic chamber was 1905 ± 400 kcal/d, i.e. ~1.3-fold the measured resting metabolic rate (by Deltatrac II metabolic cart). Energy balance was slightly negative, although it was not different from zero (-90 ± 270 kcal/d; $p = 0.09$). Over the 24-h period, RQ was 0.90 ± 0.03 , i.e. ~2% (0.02 ± 0.03 ; $p = 0.02$) higher than the “food quotient” (0.88) (Table 2). However, RQ was not related to energy balance ($r = 0.25$; $p = 0.22$).

Correlations between non-protein RQs (fasting, OGTT and 24 hours) and insulin sensitivity (by clamp) are shown in Table 3. Non-protein RQ over 24 hours was positively associated with insulin sensitivity ($p = 0.03$); although after controlling for energy balance, this association lost statistical significance ($r = 0.36$; $p = 0.07$). In turn, fasting and glucose-stimulated non-protein RQs did not correlate with insulin sensitivity. Fasting non-protein RQ correlated directly with OGTT non-protein RQ ($p = 0.03$; Table 3), but not with 24-h non-protein RQ ($p = 0.73$; Table 3). Mean OGTT and 24-h non-protein RQs were related to each other ($p = 0.02$; Table 3).

3.2 Insulin secretion and β -cell function

As expected, both fasting and glucose-stimulated insulin secretion rates (from deconvolution of serum C-peptide concentration) correlated with 24-h insulin secretion from urinary C-peptide adjusted for total energy intake ($p < 0.001$; Table 3). Furthermore, the often reported inverse association between insulin sensitivity and insulin secretion was confirmed. This association was the strongest between 24 hours insulin secretion and insulin sensitivity, followed by OGTT and fasting insulin secretion rates (Table 3). On the other hand, β -cell function did not correlate with insulin sensitivity (Table 3).

3.3 Fuel oxidation and insulin secretion parameters

We first tested the correlations of non-protein RQs (fasting, OGTT and 24 hours) vs. insulin secretion rates (fasting, OGTT and 24 hours) (Table 3). An inverse significant association between 24-h non-protein RQ and 24-h insulin secretion was found (Table 3 and Figure 2), which remained significant after controlling for potential confounders such as energy balance, age, body mass index and insulin sensitivity. In a multivariate regression model including insulin sensitivity and 24-h non-protein RQ as determinants of 24-h insulin secretion, both insulin sensitivity and 24-h non-protein RQ were statistically significant ($R^2 = 0.55$, $p < 0.02$ for both factors; log-transformed data).

Similar analyses were conducted between the absolute amount of carbohydrate stored (intake minus oxidation) and oxidized over 24 hours (in grams per kg of EMBS). Consistent with our hypothesis, insulin secretion rate estimated from urinary C-peptide was related to carbohydrate balance ($r = 0.41$; $p = 0.04$) and oxidation ($r = -0.40$; $p = 0.04$). These associations

remained unchanged after adjustment for energy balance, age, body mass index and insulin sensitivity.

Associations between non-protein RQ and insulin secretion parameters during a shorter period of time (fasting and OGTT) were also evaluated. Fasting non-protein RQ did not correlate with fasting ($p=0.79$), glucose-stimulated ($p=0.36$) or 24-h ($p=0.91$) insulin secretion (Table 3). However, fasting non-protein RQ correlated positively with rate sensitivity (Table 3), and at a weaker extent with glucose sensitivity ($p=0.08$), whereas no association was found with the potentiation factor ratio ($p=0.97$). Fasting carbohydrate oxidation (in $\text{mg}\cdot\text{min}^{-1}$ per kg EMBS) also correlated with rate sensitivity ($r=0.44$; $p=0.02$) but not glucose sensitivity ($r=0.18$; $p=0.37$). After glucose stimulation, there was no association between non-protein RQ and any of the insulin secretion parameters (Table 3).

4. Discussion

To our knowledge, this study is the first analysis of the relationships between whole-body glucose oxidation and insulin secretion. In agreement with our hypothesis, we found associations that suggest unexplored pathways in the crosstalk between peripheral tissues (e.g. skeletal muscle) and pancreas [3]. The first is an inverse relationship between 24-h non-protein RQ (an index of carbohydrate relative to lipid oxidation) and 24-h insulin secretion from urinary C-peptide; the second is a direct correlation between fasting non-protein RQ and β -cell function derived from OGTT modeling.

The inverse relationship between 24-h non-protein RQ and 24-h insulin secretion may just be a consequence of the inverse association between insulin sensitivity and insulin secretion [2], since 24-h non-protein RQ is directly related to insulin sensitivity. However, it is noteworthy that this finding was still present after adjusting for insulin sensitivity as well as for energy balance, age and body mass index. Thus, beyond the well-known role of insulin sensitivity, 24-h non-protein RQ appears to be an independent factor associated with insulin secretion.

Surprisingly, such outcome was only true after a 24-h period, but not in fasting or short-term glucose-stimulated conditions. C-peptide excretion is determined by its secretion and renal clearance [17], while serum C-peptide concentration, particularly over a short period of time, is mostly related to its secretion. The eventual (non-tested) influence of fuel oxidative partitioning on renal C-peptide clearance might play a role.

The direct relationship between fasting non-protein RQ and OGTT-derived β -cell function provides for the first time some evidence that fuel oxidative partitioning may interact with β -cell function. Indeed, a significant direct association was detected for rate sensitivity (a marker of early glucose-stimulated insulin secretion), while with glucose sensitivity it did not reach significance. The mechanisms underlying the interaction between fuel oxidative partitioning, particularly under fasting conditions, with rate sensitivity remain to be elucidated. One may speculate that the extent to which glucose is oxidized may play a role in glucose sensing, particularly in early rather late phases of insulin secretion. In our protocol, first-phase insulin secretion is better represented by the fasting gas exchange

measurement; because the earliest postprandial fuel oxidative assessment started 40 min after glucose ingestion.

We also found that 24-h insulin secretion (from urinary C-peptide excretion) was correlated with fasting ($r=0.66$) and OGTT ($r=0.64$) insulin secretion (both from serum C-peptide). The presence or absence of the nutritional stimulus appeared to have little influence since in both fasting or in response to oral glucose, the relations were unchanged. The lack of a stronger correlation between our insulin secretion estimates (24 hour vs. fasting/OGTT) may lie on the fact that insulin secretion rates were determined on two different, but consecutive days. Potential influence of the preceding diet, physical activity, energy balance, among other factors may have contributed to inter-day variations in insulin secretion. In addition, both methods covered different time periods (i.e. 4 vs. 24 hours), and it is known that insulin secretion fluctuates throughout the day even when the same nutritional stimulus is provided [18].

Finally, C-peptide excretion depends on both renal C-peptide uptake and clearance [17, 19]. On average, ~25% of arterial C-peptide is filtered by the kidneys. Most of the filtered C-peptide is degraded to amino acids, while the remaining (6-24%) is excreted into the urine [18]. A better concordance between serum and urinary C-peptide markers may require to perform both assays on the same day and to include a measure of renal C-peptide clearance.

Further research is imperative to overcome the descriptive nature of our reported correlations. The identification of causal relationships between tissue-specific glucose flux (i.e. uptake, oxidation or storage) and insulin secretion is needed, followed by the identification of putative cellular pathways and circulating mediators involved. In addition, 24-h assessment of insulin secretion by urinary C-peptide excretion should include correction for renal C-peptide clearance.

In conclusion, we have described for the first time associations between energy substrate oxidative metabolism and insulin secretion under different nutritional conditions in non-diabetic individuals. Our main finding highlights a possible effect of 24-h carbohydrate oxidation on insulin secretion with a concomitant stimulating effect of fasting carbohydrate oxidation on β -cell glucose sensing. The first finding should be easily corroborated (or dismissed) from the many metabolic chamber data already available in which urine must be necessarily collected for nitrogen analysis. Specific assessment of skeletal muscle metabolism will be necessary to confirm the findings and lead to identify a mechanistic link between peripheral glucose flux and insulin secretion. Those studies should contribute to clarify the physiological relevance of a potential crosstalk between skeletal muscle and pancreas in the regulation of insulin secretion.

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Abbreviations

EMBS	estimated metabolic body size
FFM	fat free mass
npRQ	non-protein respiratory quotient
OGTT	oral glucose tolerance test
PFR	potentiation factor ratio
GDR	glucose disposal rate
DXA	Dual-energy X-ray absorptiometry

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Highlights

- Insulin-mediated glucose disposal relates inversely with insulin secretion
- Skeletal muscle fuel metabolism seems to influence insulin secretion
- 24-h whole-body fuel oxidative partitioning determined 24-h insulin secretion
- Fasting fuel oxidation was associated with specific beta cell function parameters

Figure 1. Experimental design
OGTT: Oral glucose tolerance test
DXA: Dual-energy X-ray absorptiometry

Figure 2. Association between 24-h non-protein respiratory quotient and 24-h insulin secretion rate

Insulin secretion rate corresponds to 24-h urinary C-peptide excretion corrected by the amount of ingested energy. Relation between variables was assessed with Spearman's correlation analysis. Partial Spearman's correlation analysis ($r=-0.52$; $p=0.01$ adjusted for energy balance, age, body mass index and insulin sensitivity).

Table 1

Characteristics of participants.

	Mean $\pm$ SD	Range
Male/female	15/15	–
Age (years)	35.4 $\pm$ 11.5	18.7 – 53.6
Body mass (kg)	78.8 $\pm$ 15.2	57.1 – 107.8
Body mass index (kg/m ²)	27.2 $\pm$ 4.0	21.6 – 34.2
Body fat (%)	28.8 $\pm$ 8.7	10.4 – 48.0

Table 2

Parameters of glucose metabolism and insulin secretion.

	Mean $\pm$ SD	Range
Glucose disposal rate (mg [kg EMBS] ⁻¹ min ⁻¹)	7.3 $\pm$ 2.6	3.6 – 13.2
Fasting non-protein RQ	0.84 $\pm$ 0.03	0.79 – 0.90
Mean OGTT non-protein RQ	0.91 $\pm$ 0.04	0.85 – 0.98
24-h non-protein RQ	0.91 $\pm$ 0.04	0.82 – 0.98
Fasting insulin secretion (pmol·min ⁻¹ ·m ⁻²)	89 $\pm$ 36	35 – 171
OGTT insulin secretion (nmol·m ⁻²)	80 $\pm$ 33	32 – 183
Glucose sensitivity (pmol·min ⁻¹ ·m ⁻² ·mM ⁻¹)	119 $\pm$ 47	40 – 277
Rate sensitivity (pmol·m ⁻² ·mM ⁻¹)	1609 $\pm$ 1471	0 – 6865
Potential factor ratio	1.49 $\pm$ 0.56	0.62 – 2.93
24-h C-peptide excretion/kcal ingested (μg·kcal ⁻¹)	52 $\pm$ 27	20 – 145

Glucose disposal rate measured by euglycemic-hyperinsulinemic clamp; EMBS, estimated metabolic body size (fat-free mass in kg + 17.7); OGTT, 75-g oral glucose tolerance test; RQ, respiratory quotient; Potential factor ratio between 120 min post-OGTT and baseline.

Table 3

Spearman correlations between pancreatic insulin secretion and β -cell function with whole-body non-protein respiratory quotient.

	Insulin sensitivity		Non-protein RQ		Insulin secretory rate		Glucose sensitivity	Rate sensitivity
	Fasting	OGTT	24 h	Fasting	OGTT	24 h		
Insulin sensitivity	–							
Fasting npRQ	0.06	–						
OGTT npRQ	0.18	0.42 *	–					
24-h npRQ	0.42 *	0.08	0.47 *	–				
Fasting ISR	–0.40 *	0.05	–0.26	–				
OGTT ISR	–0.50 [†]	–0.18	–0.11	0.72 [†]	–			
24-h ISR	–0.62 [†]	0.02	–0.26	0.66 [†]	0.64 [†]	–		
Glucose sensitivity	0.02	0.34	0.08	–0.12	0.02	0.06	–	
Rate sensitivity	–0.22	0.40 *	0.16	0.49 [†]	0.46 *	0.23	0.22	–
PFR	0.29	–0.01	–0.11	0.13	–0.13	–0.26	0.40 *	–0.36

Insulin sensitivity corresponds to glucose disposal rate measured by euglycemic-hyperinsulinemic clamp; npRQ, non-protein respiratory quotient; ISR, insulin secretion rate by Mari's model (fasting and OGTT [oral glucose tolerance test]) and urinary C-peptide excretion corrected by energy intake; PFR, potentiation factor ratio between 120 min post-OGTT and baseline. Significant associations are displayed in bold.

* p<0.05

[†] p<0.01