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THE USE OF HOMA-IR AND QUICKI IN RODENT DIABETIC MODEL: SHORT COMMUNICATION

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ABSTRACT

Regarding *diabetes mellitus* type 2 (DMT2) in animal research, a non-invasive and less traumatic method, such as the mathematic calculation of indexes expressing the insulin sensitivity and resistance, is required. There are some methods and formulas for calculation and estimation of insulin resistance. The most well-known validated methods are the homeostatic model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI), which are suitable for clinical and research purposes. The goal of this study was to calculate HOMA-IR and QUICKI indexes in an experiment with Zucker diabetic fatty (ZDF) rats fed normal or high-energy diet. Additionally, the correlations between both models were inquired. Animals were divided into three groups: lean untreated control rats (C, n = 10) fed a complete feed mixture for rats and mouse (10 MJ.kg^{-1}), diabetic rats fed the same chow (E1, 10 MJ.kg^{-1}) and diabetic rats fed high energy diet (E2, enriched KKZ-P/M, 20 MJ.kg^{-1}). After overnight fasting, the rats were monitored for blood glucose level by a FreeStyle Optium Neo Glucose and Ketone Monitoring System (Abbott Diabetes Care Ltd., UK) using test strips. An ELISA commercial kit (Biotech, Bratislava, Slovak Republic) was used to measure the serum content of insulin. Values of fasting plasma insulin and serum glucose were used to calculate HOMA-IR and QUICKI indexes. HOMA-IR and QUICKI significantly differed among the groups. Strong negative correlations were found in dependence on the diet. This study indicated that the calculation of HOMA-IR and QUICKI can potentially be an effective tool in determination, evaluation, onset and progress of DMT2.

Key words: HOMA-IR; QUICKI; diabetes; Zucker diabetic fatty rats; diet

INTRODUCTION

Insulin resistance is considered a major risk in the ethology of diabetes mellitus second type (DMT2; Bray, 2004). It is a predictor for the onset and development of DMT2 even in patients with normal level of serum glucose. Therefore, it is very useful to determine insulin resistance in the pre-diabetic stage because at this point the treatment and therapy of DM is more successful than in the developed disease (Boden, 2001). Generally, insulin resistance refers to a state in which cells of peripheral tissues have a reduced level of response to insulin (Choi and Kim, 2010).

HOMA and QUICKI models

Both models are the most widely applied in the case of assessing insulin sensitivity. They are based on fasting glucose and insulin values. These two models mainly differ by the log transformation of the variables in QUICKI, and the constant denominator in HOMA (Antuna-Puente *et al.*, 2008).

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Homeostatic Model Assessment of Insulin Resistance

Homeostatic model assessment of insulin resistance (HOMA-IR) was developed in 1985 by Matthews *et al.* (1985). It is a method for quantification of insulin resistance and β-cell function from fasting serum glucose and insulin concentrations (Gutch *et al*., 2015). The model has been generally used since it was first published (Wallace *et al.*, 2004). It is induced from the use of the insulin-glucose product, divided by a constant according to the formula (Haffner *et al.*, 1997):

$$HOMA\text{-}IR = \frac{\text{serum insulin (mmol.L}^{-1}\text{)} * \text{blood glucose (mmol.L}^{-1}\text{)}}{22.5}$$

Quantitative Insulin Sensitivity Check Index

Quantitative insulin sensitivity check index (QUICKI) is an empirically-derived mathematical transformation of fasting serum glucose and insulin concentrations that gives consistent information about insulin sensitivity with a predictive possibility. It can be calculated from fasting serum glucose and insulin concentrations (Chen *et al*., 2003; Gutch *et al.*, 2015) QUICKI is a variation of HOMA equations, as it transforms the data by using both the logarithm and the reciprocal of the glucose-insulin product, so slightly canting the distribution of fasting insulin values (Chen *et al*., 2003).

$QUICKI = 1/(\log I_0 + \log G_0)$,

where I_0 means fasting insulin and G_0 – fasting glucose.

Some studies showed that HOMA is less reproducible than QUICKI (Sarafidis *et al.*, 2007). This is probably due to the normalization by logarithmic transformation of the data. But, log HOMA did not increase its reproducibility (Antuna-Puente *et al*., 2008). Alternatively, HOMA could be more sensitive to variations in insulin values (Antuna-Puente *et al*., 2008), what occurs mainly in individuals suffering from DM2T. In this case HOMA index appears to be a very suitable method. The given biological variability of insulin values is the main source of variation.

The applicability of HOMA-IR and QUICKI in experimental research is questioned due to the lack of data for validation in most animal species (Wallace *et al*., 2004). Therefore, the aim of this report was to determine HOMA-IR and QUICKI index in Zucker diabetic fatty (ZDF) rats fed a normal or high-energy diet. Additionally, the relationships between both models were inquired.

MATERIAL AND METHODS

Animals

Male Zucker diabetic fatty (ZDF) rats (a fatty *fa/fa* mutation (-/-); n = 20) and their healthy lean controls (lean, non-diabetic, +/+ or +/-, not display expression of *fa* phenotype, n = 10) of the same strain at the age of 3 months (12 weeks of age) were involved in the experiment. The animals were purchased from Breeding Facility of the Institute of Experimental Pharmacology and Toxicology (Dobra Voda, Slovak Republic, SK CH 24016). All animals were housed in number of two rats per plastic cage (80 cm^2) and under specific pathogen-free conditions at 23 ± 2 °C and 55 ± 10 % relative humidity with a 12 h light-dark cycle. Rats were provided with water and diet on *ad libitum* base.

Experimental design

Rats were divided into three groups (n = 10 each) as follows: lean rats (C) fed KKZ-P/M (a complete feed mixture for rats and mouse, reg. no 6147, Dobra Voda, Slovak Republic, 10 $MJ.kg^{-1}$), diabetic rats fed by KKZ-P/M (E1, 10 $MJ.kg^{-1}$) and diabetic rats fed high energy diet (E2, enriched KKZ-P/M, 20 $MJ.kg^{-1}$, 30 % saturated fatty acids, 5 % starch and 15 % disaccharides). The initial body weigh did not differ between rats within the same genotype (E1, E2). The experiment lasted 3 months.

Glucose analysis

At the end of the experiment after overnight fasting the rats were monitored for blood glucose level by a FreeStyle Optium Neo Glucose and Ketone Monitoring System (Abbott Diabetes Care Ltd., UK, measurable extent 1.1 – 27.8 $mmol.l^{-1}$ (20 - 500 $mg.dl^{-1}$) using test stripes (FreeStyle, Abbott Diabetes Care Ltd., UK). One drop of blood was collected from the tail vein in the morning between 7:00 to 9:00 a.m. and directly used for glucose value measurement.

Insulin analysis

At the end of the experiment, after glucose measurement the animals were anesthetized by

intraperitoneal injection with chloral hydrate (40 mg.100 g^{-1} body weight). Blood samples were collected into EDTA-treated tubes. ELISA commercial kit (Biotech, Bratislava, Slovak Republic) was used to measure the serum content of insulin according to the instruction of the manufacturer.

HOMA-IR and QUICKI determination

Values of fasting plasma insulin and serum glucose were used to calculate HOMA-IR and QUICKI indexes, as a mathematical model that includes interactions between fasting serum insulin and blood glucose concentration.

Statistical analysis

Data are expressed as mean ± SD (standard deviation). One-way ANOVA test was performed to calculate basic statistical characteristics and to determine significant differences. A SAS Release 9.1 statistical software (SAS Institute Inc. Cara, USA, 2002-2003) was used. Pearson correlation coefficient was used to determine correlations between the methods. Differences were compared for statistical significance at the levels $P < 0.001$, 0.01, and 0.05.

RESULTS AND DISCUSSION

A proper estimation of insulin resistance is needed due to its key role in the pathophysiology of DMT2 (Choi and Kim, 2010). Various tools for quantifying insulin sensitivity and resistance directly and indirectly were reported (Mari *et al.*, 2001). Animal model of ZDF rat is a relevant tool that mirrors the pathogenesis of DMT2 in humans (Capcarova e*t al*., 2018a; Capcarova *et al*., 2018b). In our study we calculated HOMA-IR and QUICKI indexes. HOMA represents the glucose-insulin homeostasis by means of a set of elementary, mathematically-derived nonlinear equations (Matthews *et al*., 1985). QUICKI was determined from fasting serum glucose and insulin values (Table 1). The HOMA model is frequently used as a useful tool in clinical and epidemiological studies for descriptions of the pathophysiology of DMT2. It facilitates determination of inherent β-cell function and insulin sensitivity and can explain the pathophysiology in those with abnormal glucose tolerance (Wallace *et al*., 2004). Values less than 2.5 are reported as normal values (Gutch *et al.*, 2015). Mean HOMA-IR in this study (Figure 1) was the lowest in the lean group (1.37 ± 0.08), followed by the group on a normal diet (2.24 ± 0.29) and the highest values were measured in the group fed high-energy diet (5.31 ± 0.46). Significant differences were noted between lean and energy diet, between normal and energy diet ($P < 0.001$) and between lean and normal diet ($P < 0.05$).

Very similar results were obtained by Antunes *et al.* (2016) in the study with a model of insulin-resistance induced by high-fat diet in Wistar rats (2.32 ± 0.75 normal diet and 4.58 ± 1.85 high-fat diet) with significant differences between both groups. The authors confirmed that HOMA-IR has a strong correlation with the insulin tolerance test and may be used as a surrogate marker of insulin resistance in rats. Appleton *et al.* (2002) considered HOMA-IR for the most useful predictor of insulin resistance.

The values of QUICKI reported by Gutch *et al.* (2015) were 0.382 ± 0.007 for non-obese, 0.331 ± 0.010 for obese individuals and 0.304 ± 0.007 for diabetic patients. In our study we found similar

Table 1. Fasting glucose and insulin values in ZDF rats

Parameter	Group		
	Lean	Diabetic normal diet	Diabetic high-energy diet
Glucose (mmol.l^{-1})	3.89 ± 0.08^{a}	9.56 ± 1.08^{b,A}	15.54 ± 1.16^{b,B}
Insulin (µg. l^{-1})	7.72 ± 0.477^{a}	5.24 ± 0.40^{b}	5.13 ± 0.19^{b}

$^{a-b}$ or $^{A-B}$ mean significant difference ($P < 0.001$) in rows

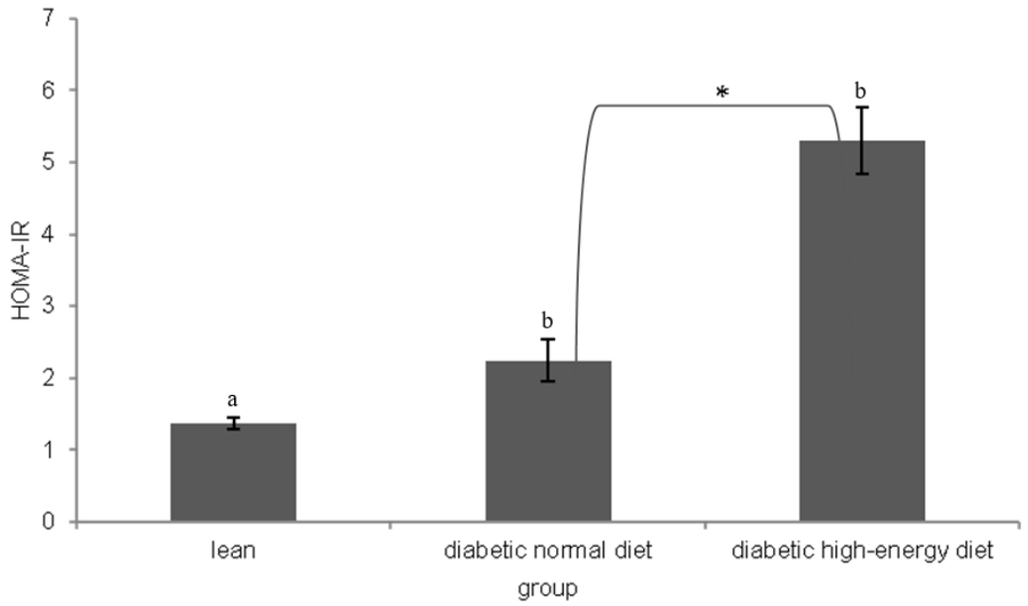

Figure 1. Homeostatic model assessment of insulin resistance (HOMA-IR) in ZDF rats
[a-b] mean significant difference (P < 0.05; P < 0.001) among the groups
[*] means significant differences (P < 0.001) between diabetic groups

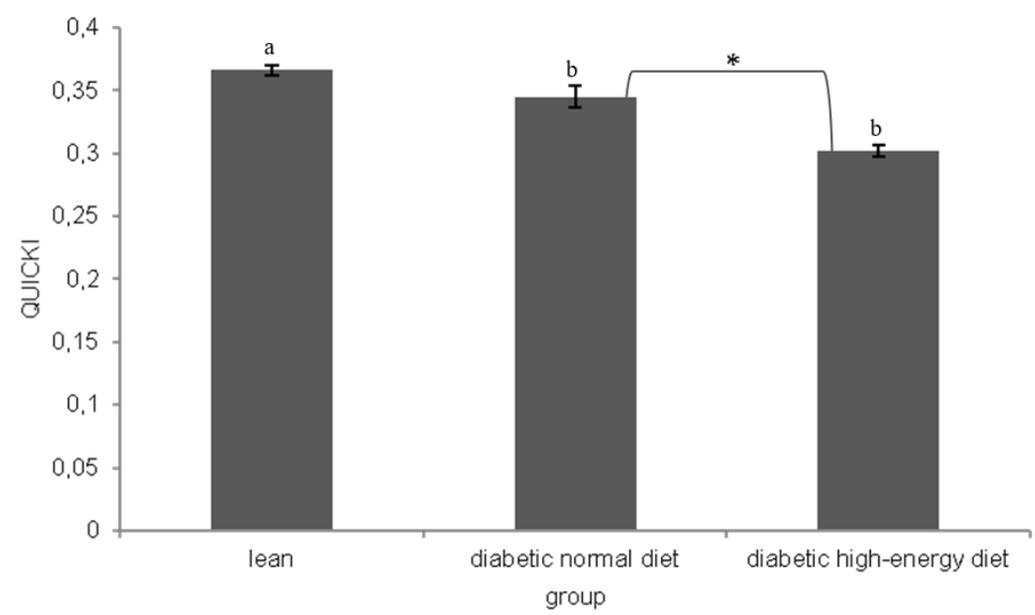

Figure 2. Quantitative insulin sensitivity check index (QUICKI) in ZDF rats
[a-b] mean significant difference (P < 0.05; P < 0.001) among the groups
[*] means significant differences (P < 0.001) between diabetic groups

Table 2. Pearson correlation coefficients between HOMA-IR and QUICKI model in ZDF rats

	Normal diet QUICKI	Energy diet QUICKI	Lean HOMA-IR	Normal diet HOMA-IR	Energy diet HOMA-IR
Lean QUICKI	0.559	-0.394	**-0.967**	-0.564	0.349
Normal diet QUICKI		-0.432	-0.508	**-0.955**	0.366
Energy diet QUICKI			0.384	0.446	**-0.985**
Lean HOMA-IR				0.537	-0.344
Normal diet HOMA-IR					-0.362
Energy diet HOMA-IR					1

0-0.33 – weak correlation, 0.34-0.66 – medium correlation, **0.67-1 – strong correlation**

values for non-obese and non-diabetic lean rats 0.366 ± 0.004 (Figure 2). In diabetic rats, the values were: 0.345 ± 0.009 – in the diabetic group and 0.302 ± 0.005 – in the diabetic group with high-energy diet. The differences among the groups were significant ($P < 0.001$ and $P < 0.05$). Similar data (0.30 ± 0.02 and 0.31 ± 0.02) were reported by Sarafidis *et al.* (2007) in study with patients suffering DMT2. The values less than 0.4 are considered normal and within the physiological range (Gutch *et al*., 2015).

In this study we found significantly high correlation ($r = -0.97$; $r = -0.96$; and $r = -0.99$; $P < 0.0001$) between HOMA-IR and QUICKI in all groups of animals (Table 2) depending on the diet. QUICKI is recognized as simply being log HOMA-IR, which interprets the high correlation with HOMA (Wallace *et al*., 2004). QUICKI was strongly correlated with insulin resistance index determined by euglycemic-hyperinsulinemic clamp, which is the most used standard method in the type 2 diabetic patients (Yokoyama *et al*., 2003).

The eventuality of evaluating insulin sensitivity and resistance in animals using a simpler and less traumatic method is important for experimental research (Antunes *et al*., 2016). Both, HOMA and QUICKI have been fully validated in human studies. In animal research it is important to focus and improve insulin and glucose measurement in order to use these methods. Generally, the determination by both methods in animal studies has advantages. They are simple methods with no need in special expertise, causing minimal stress to individuals, and practically free from the risk of hypoglycaemia (Antunes *et al.*, 2016). HOMA-IR and QUICKI indexes of insulin resistance founded on fasting measurements of insulin and glucose can serve as practical and useful surrogate of more complicated and time-consuming clamp-based measurements (Mather, 2019).

To conclude, this study indicated that the calculation of HOMA-IR and QUICKI can potentially be an effective tool in determination, evaluation, onset and progress of DMT2. Further studies are still needed to standardize the method and for better understanding and interpretation of the data in rodent experiments.

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