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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1396 – 1401
Metabolism
Clinical and Experimental
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Assessment of non–insulin-mediated glucose uptake: association with body fat and glycemic status

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Received 5 November 2009; accepted 8 January 2010

Abstract

In the fasting state, approximately 83% of glucose uptake occurs via non–insulin-mediated mechanisms. A widely accepted static rate for NIMGU is 1.62 mg $kg^{-1}\cdot min^{-1}$. To investigate the variability of NIMGU, we examined differences by glucose tolerance, sex, age, race (American Indian/African American/Caucasian), and adiposity in 616 volunteers (including individuals with normal glucose regulation [NGR] and impaired glucose regulation [IGR] and diabetes mellitus [DM]) using data from euglycemic-hyperinsulinemic clamp experiments. NIMGU was determined by plotting basal glucose output and insulin action against fasting and steady-state clamp insulin. The intercept with the y-axis after extrapolation was interpreted as NIMGU at zero insulin. Body composition was determined by dual-energy x-ray absorptiometry; and glucose regulation, by a 75-g oral glucose tolerance test. Energy expenditure was measured by indirect calorimetry in a metabolic chamber. In individuals with NGR (n = 385), NIMGU was 1.63 mg $kg^{-1}_{\text{estimated metabolic body size (fat free mass + 17.7 kg)}}$ min^{-1} (95% confidence interval, 1.59-1.66). NIMGU increased with IGR and DM (IGR: n = 189, 1.67 [1.62-1.72]; DM: n = 42, 2.39 [2.29-2.49]; $P < .0001$ across groups). NIMGU did not differ by sex ($P = .13$), age ($P = .22$), or race ($P = .06$); however, NIMGU was associated with percentage body fat ($r^2 = 0.04$, $P < .0001$). Furthermore, NIMGU was positively associated with 24-hour and sleep energy expenditure ($r^2 = 0.002$, $P = .03$; $r^2 = 0.01$, $P < .01$). Extrapolated NIMGU in individuals with NGR is remarkably consistent with previously published data. Our results indicate that NIMGU is associated with adiposity. NIMGU increases with declining glucose tolerance perhaps to preserve glucose uptake during increased insulin resistance.
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1. Introduction

In the human body, glucose uptake is accomplished via 2 mechanisms, insulin-mediated glucose uptake (IMGU), which occurs only in insulin-sensitive tissues (ie, liver, muscle, and adipocytes), and non–insulin-mediated glucose uptake (NIMGU), which occurs in both insulin-sensitive and non–insulin-sensitive tissues (ie, brain, blood cells, nerve, etc). As early as 1934, Soskin et al [1] provided evidence for a mechanism of glucose disposal independent of insulin in pancreatectomized dogs. In experimental models, *NIMGU* has been defined as uptake of glucose at zero insulin concentrations [2]. In the fasting state, NIMGU accounts for about 83% of whole-body glucose disposal [3]. Gottesman et al [4] investigated NIMGU in 16 lean nondiabetic individuals via various insulin infusions after somatostatin-induced suppression of endogenous insulin release. In the euglycemic state, NIMGU was 1.62 mg $kg^{-1}\cdot min^{-1}$, which became a widely accepted static rate for NIMGU [4]. How the rate of NIMGU might change in the presence of hyperglycemia is unclear. Forbes at al [5] reported a significantly lower rate of NIMGU in patients with type 2 diabetes mellitus compared with healthy controls. However, others report no significant differences in NIMGU in diabetic vs nondiabetic patients at similar glucose levels [6,7]. In contrast, Capaldo et al [8] demonstrated that hyperglycemia increased insulin-independent peripheral glucose disposal in individuals with diabetes vs controls. In most

Institutional approval: The protocol and consent were approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases.

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0026-0495/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.metabol.2010.01.006

of these studies, NIMGU was assessed via suppression of endogenous insulin with somatostatin; however, these studies all involved a small number of study subjects.

We assessed NIMGU rates by extrapolation of clamp data in 616 volunteers and examined differences by glucose tolerance, sex, age, race, and adiposity in a population of American Indians, African Americans, and Caucasians. Because glucose-induced glucose uptake (via mass action) might be expected to induce futile cycles (such as the Cori cycle) that would influence metabolic rate [9], we investigated whether NIMGU was also related to energy expenditure (EE).

2. Methods

Volunteers participated in a longitudinal study of predictors of type 2 diabetes mellitus. All subjects were free of other medical diseases as determined by laboratory testing, history, and physical examination. Subjects were not taking any medications and were nonsmokers. Volunteers were admitted to the clinical research unit and placed on a weight-maintaining diet for at least 3 days before any metabolic testing. For this substudy analysis, 616 subjects were selected who had complete data for anthropometry as measured by dual energy x-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI), glucose regulation status determined by oral glucose tolerance testing (OGTT), and insulin action (M) evaluated using the hyperinsulinemic-euglycemic glucose clamp technique. All subjects provided written informed consent. The protocol and consent were approved by the Institutional Review Board of the National Institute of Diabetes Digestive and Kidney Disease.

2.1. Oral glucose tolerance test

After an overnight fast, subjects were given a 75-g oral glucose load. Blood samples were drawn at 0 (G0), 30 (G30), 60 (G60), 120 (G120), and 180 (G180) minutes for measurement of plasma glucose and insulin concentrations. According to results of the OGTT, subjects were categorized as either having normal glucose regulation (NGR; fasting plasma glucose [FPG] <5.6 mmol/L and 2-hour plasma glucose [2hPG] <7.8 mmol/L), impaired glucose regulation (IGR; FPG ≥5.6 mmol/L and <7.0 mmol/L and/or 2hPG ≥7.8 mmol/L and < 11.1 mmol/L), or type 2 diabetes mellitus (DM; FPG ≥7.0 mmol/L and/or 2hPG ≥11.1 mmol/L) per American Diabetes Association 2003 criteria [10]. Incremental area under the curve (iAUC) for glucose was calculated as follows: {[(G0 + G30)/2]∗30} + {[(G60 + G120)/2]∗60} + {[(G120 + G180)/2]∗60} − (G0∗G180). Plasma insulin concentrations were measured by 3 different radioimmunoassays used over time in our laboratory: modified Herbert-Lau assay [11], Concept 4 (Concept 4; ICN, Costa Mesa, CA), and Access (Beckman Instruments; Fullerton, CA) insulin assays. All measurements of insulin were normalized to the original radioimmunoassay (modified Herbert-Lau assay) using regression equations. Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Instruments).

2.2. Hyperinsulinemic-euglycemic glucose clamp

Details of the insulin clamp technique have been previously described [12]. Briefly, after an overnight fast, a catheter was placed in the antecubital vein; and a primed (1.11 MBq) continuous (0.0111 MBq/min) 3-[^{3}H] glucose infusion was started to determine endogenous glucose production (EGP). Two hours after beginning infusion of the 3-[^{3}H] glucose, a primed continuous insulin infusion was administered at the rate of 40 mU m^{-2} min^{-1} for 100 minutes. After the start of the insulin infusion, plasma glucose concentrations were measured every 5 minutes; and a variable infusion of 20% dextrose was used to maintain glucose at 5.6 mmol/L. Basal glucose output (BGO) was calculated during the fasting state as the 3-[^{3}H] glucose infusion rate divided by the steady-state plasma 3-[^{3}H] glucose specific activity (measured with Beckman LS6500 scintillation counter; Beckman Instruments). During the insulin clamp, EGP was calculated from the Steele non–steady state [13]. The rate of glucose disposal (M) was defined as the average sum of glucose infusion rate and EGP during the last 40 minutes of the insulin infusion and was corrected for both steady-state plasma insulin levels and EGP. The M values were normalized to estimated metabolic body size (EMBS; fat free mass + 17.7 kg) [14].

2.3. Measurement of EE

Energy expenditure was measured in the respiratory chamber as previously described [15]. Briefly, after an overnight fast, study volunteers entered the chamber at 6:45 AM and remained therein for 23 hours. Meals were provided at 8:00 AM, 11:30 AM, 5:00 PM, and 8:00 PM. Energy content of provided meals was only 80% of the weight-maintaining diet because of the confinement within the chamber. During constant flow of fresh air through the chamber, CO_2 production and O_2 consumption were measured and calculated every 15 minutes and extrapolated for a 24-hour interval. Radar sensors were used to detect spontaneous physical activity expressed as percentage of time over the 23-hour period in which activity was evaluated. *Energy expenditure during sleep* (SLEEPEE) was defined as the average EE of all 15-minute periods between 11:30 PM and 5:00 AM during which spontaneous activity was less than 1.5%.

2.4. Statistical analysis

NIMGU was determined by plotting BGO and M values (y-axis) against fasting and steady-state clamp insulin (x-axis) for each volunteer. The intercept of this line with the y-axis after extrapolation was interpreted as NIMGU, that is, the glucose uptake at zero insulin

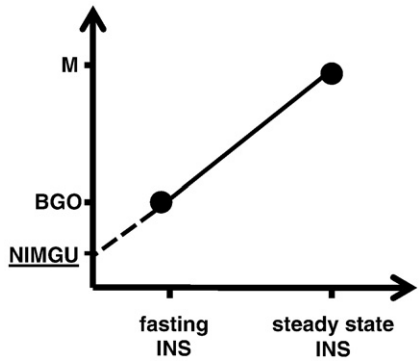

Fig. 1. Schematic diagram depicting the determination of NIMGU. By plotting BGO and M values on the y-axis against fasting and steady-state clamp insulin on the x-axis, we created 2 data points per individual. NIMGU was then determined via extrapolation of the linear slope to the intercept with the y-axis at virtually zero plasma insulin concentrations (dashed line).

concentrations (Fig. 1). Subject characteristics are depicted as mean ± SD or median (25th-75th percentile). Normally distributed variables were analyzed by Student test; and for multiple groups, by 1-way analysis of variance. Skewed variables were analyzed by the Kruskal-Wallis test. Linear regression models were used to calculate least square means and 95% confidence intervals (CIs) for NIMGU after adjusting for sex, age, race, percentage body fat (PFAT), and glucose regulation status. Linear regression models adjusted for fat mass, fat-free mass, age, race, and glucose regulation status were also used to test the association of NIMGU with EE. For comparison between multiple groups, P values were adjusted using the Tukey correction. α was set at $P < .05$.

3. Results

3.1. Subject characteristics

Anthropometric and metabolic characteristics of the 616 study volunteers are depicted in Table 1. Basal glucose output was higher in individuals with type 2 diabetes mellitus compared with individuals with NGR or IGR. Basal glucose output was lowest in American Indians and highest in African Americans and was higher in women compared with men. Fasting insulin concentrations were higher in women and American Indians and increased with worsening glucose tolerance. Steady-state clamp insulin concentrations were highest in American Indians and lowest in Caucasians. As expected, M was lower in American Indians and individuals with type 2 diabetes mellitus. In regression models, BGO was positively and M was negatively associated with PFAT (data not shown).

3.2. Non–insulin-mediated glucose uptake

NIMGU was lowest in the NGR group and increased with worsening glucose regulation status (NGR [n = 385], 1.63 mg $kg^{-1}_{EMBS}\cdot min^{-1}$ [95 % CI, 1.59-1.66]; IGR [n = 189], 1.67 mg $kg^{-1}_{EMBS}\cdot min^{-1}$ [95 % CI, 1.62-1.72]; DM (n = 42), 2.39 mg $kg^{-1}_{EMBS}\cdot min^{-1}$ [95 % CI, 2.29-2.49], $P = < .0001$ for trend across groups) (Fig. 2). NIMGU did not differ

Table 1
Characteristics of study subjects

	Sex		P	Race			P	Glucose regulation			P
	Male	Female		American Indian	African American	Caucasian		NGR	IGR	DM	
n	353 [13]	263 [29]	–	470 [40]	35 [0]	111 [2]	–	385	189	42	–
Age (y)	28 ± 7	26 (22-31)	NS	27 ± 6	26 (22-31)	29 ± 7	****	25 (21-31)	29.6 ± 6.2	28.3 ± 6.4	****
BMI (kg/m^2)	33.0 ± 7.7	35.6 ± 8.6	****	34.6 ± 7.8	32.0 ± 7.7	33.0 ± 9.5	NS	32.2 ± 7.7	37.0 ± 8.4	38.5 ± 6.3	****
PFAT (%)	27.9 ± 7.9	39.2 (35.3-43.3)	****	33.6 ± 8.4	25.6 ± 9.3	29.3 ± 10.5	****	30.0 ± 9.1	35.7 ± 8.2	38.6 ± 6.2	****
FPG[a] (mmol/L)	4.9 ± 0.7	5.4 ± 1.2	**	5.2 ± 1.1	5.0 ± 0.4	5.0 ± 0.5	NS	4.8 ± 0.4	5.4 ± 0.5	7.2 ± 2.3	****
2hPG[a] (mmol/L)	6.7 ± 2.2	8.1 ± 3.0	****	7.6 ± 2.8	6.1 ± 1.7	6.4 ± 1.7	**	6.0 (5.2-6.8)	8.4 ± 1.4	14.4 ± 3.1	****
FPI[a] (pmol/L)	236 ± 132	292 ± 146	**	278 ± 139	125 (104-222)	171 (111-236)	****	195 (132-271)	297 (195-392)	410 ± 160	****
SSPI[a] (pmol/L)	958 ± 285	1035 ± 333	*	1021 ± 313	847 (757-944)	833 (695-1028)	**	952 ± 306	1056 ± 313	1097 ± 264	****
BGO[a] (mg $kg^{-1}_{EMBS}\cdot min^{-1}$)	1.9 ± 0.3	2.0 ± 0.4	**	1.9 ± 0.3	2.1 ± 0.2	2.0 ± 0.3	****	1.9 ± 0.3	1.9 ± 0.3	2.3 ± 0.6	****
M[a] (mg $kg^{-1}_{EMBS}\cdot min^{-1}$)	2.8 (2.2-3.9)	2.7 (2.2-3.2)	NS	2.5 (2.1-3.1)	4.0 ± 1.4	3.8 ± 1.4	****	3.0 (2.4-4.0)	2.2 (2.9-2.8)	2.1 ± 0.4	****

Variables are depicted as mean ± SD or median (25th-75th percentile). Numbers in brackets represent diabetic individuals. BMI indicates body mass index; FPI, fasting plasma insulin; SSPI, clamp steady-state plasma insulin; NS, not significant ($P > .05$).

[a] P values are adjusted for glucose regulation status in sex and race groups because of the skewed distribution of diabetic individuals.

* $P < .05$.

** ≤ .01.

**** $P \leq .0001$.

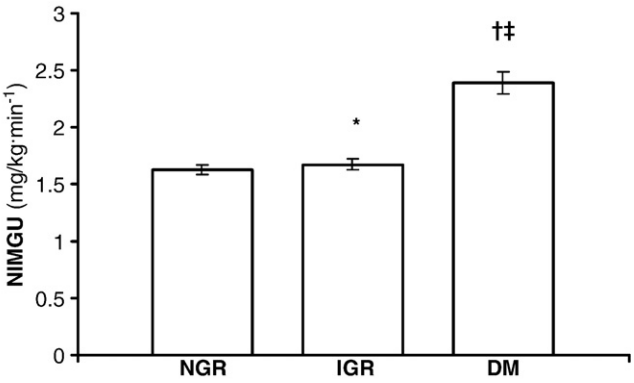

Fig. 2. Mean NIMGU in individuals with NGR, IGR, and DM. Error bars show 95% CI. *Not significant vs NGR. †$P < .0001$ vs NGR. ‡$P < .0001$ vs IGR.

significantly between NGR and IGR groups ($P = .17$) but was significantly higher in the DM group compared with NGR and IGR groups ($P < .0001$ for each comparison). Within the NGR group, iAUC during the OGTT was a significant positive determinant of NIMGU ($P < .01$). In the whole cohort, NIMGU did not differ by sex ($P = .13$), age ($P = .22$), or race ($P = .06$). However, NIMGU was significantly positively associated with PFAT ($r^2 = 0.04$, $P < .0001$, Fig. 3). To further explore an association to body fat distribution, we included waist, thigh circumference, and waist to thigh ratio, respectively, in the model instead of PFAT. No significant association was found. In the subset of individuals with measurements of EE (n = 342: NGR = 219, IGR = 102, DM = 21), NIMGU was positively associated with 24EE and SLEEPEE (additional r^2 explained over the reduced model = 0.002, $P = .03$; $r^2 = 0.01$, $P < .01$). Furthermore, in models adjusted for age and sex, higher NIMGU predicted the development of diabetes (hazard rate ratio, 2.45 [1.10-5.46], $P = .03$). However, including PFAT in the model showed that

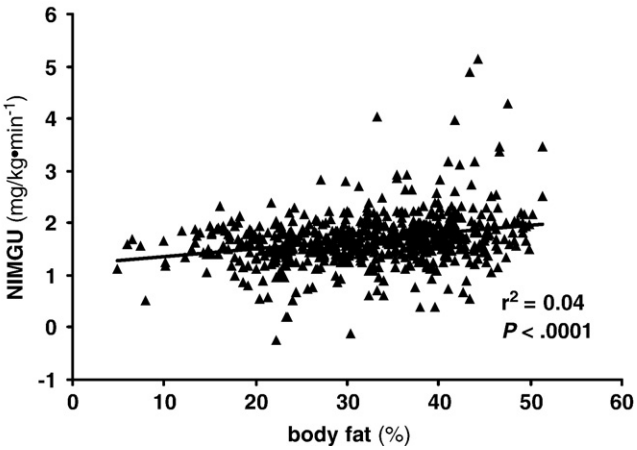

Fig. 3. Association of NIMGU and body fat in the whole study cohort (616 individuals).

NIMGU as a predictor of type 2 diabetes mellitus is partially dependent on PFAT (hazard rate ratio, 1.95 [0.87-4.34]; $P = .10$).

4. Discussion

In this large data set, including American Indians, African Americans, and Caucasians, we found that extrapolated NIMGU in the NGR group was strikingly similar to that measured in previous studies. Non–insulin-mediated glucose uptake increased with worsening glucose regulation; was associated with body fat, but not age; and did not differ by sex or race.

A limitation of our approach is that the calculation of NIMGU was an extrapolation to zero insulin concentrations based on BGO and M values plotted against respective insulin concentrations. Because each NIMGU (intercept on the y-axis) is dependent on only 2 points per individual, greater variation in one variable (in this case, the M value) would more greatly affect the value of the intercept. Specifically, a relatively greater decline in M as may occur with increased adiposity or worsening glucose tolerance would result in a higher intercept. In those with DM, the intercept would be expected to increase even more as BGO increases. However, our results for NIMGU in NGR subjects were remarkably consistent with previously published data of NIMGU assessment during somatostatin-induced insulin suppression (1.63 vs 1.62 mg $kg^{-1}\cdot min^{-1}$) [4]. Likewise, Baron et al [3] reported a similar whole-body glucose uptake of 1.83 mg $kg^{-1}\cdot min^{-1}$ at insulinopenia and euglycemia in 6 volunteers. Furthermore, this group investigated NIMGU in 7 diabetic subjects and 7 control subjects. They reported a slight elevation of NIMGU in subjects with type 2 diabetes mellitus compared with control subjects at matched plasma glucose concentrations. Although this did not reach significance, it is consistent with our observation of an increase in NIMGU in states of declining insulin sensitivity [6]. This is further supported by the positive association of NIMGU and glucose iAUC from our OGTT measurements. Moreover, NIMGU was significantly associated with both 24EE and SLEEPEE measured on a separate day from the euglycemic hyperinsulinemic clamp. Non–insulin-mediated glucose uptake would be expected to fuel futile cycles such as the Cori Cycle [9], representing the degradation of glucose to C_3-molecules with transfer of the C3-molecules back to the liver for recycling via gluconeogenesis. As an increase in futile cycling would lead to an increase in metabolic rate, the association of NIMGU with EE supports our supposition that NIMGU represents a physiologic measure of glucose uptake. A strength of our study is that this analysis was performed on a large group of individuals that would not be feasible using the method of somatostatin-induced suppression of insulin secretion. Although the nature of glucose disposal at low insulin concentrations is not yet fully explored, previous reports including one study by Gottesman et al [4] using

somatostatin to suppress insulin secretion provide evidence for a near-linear relation of glucose disposal at low plasma insulin levels [16]. Hence, given the large number of study subjects, we believe that these results further the understanding of the importance of NIMGU.

Others have evaluated insulin-independent glucose uptake using glucose effectiveness or S_g derived from the minimal model estimation [17]. When using this term, in contrast to our findings, studies in the past have illustrated that S_g was lower in diabetic individuals compared with healthy controls [18,19]. Moreover, Martin et al [20] found that lower S_g predicted the development of diabetes. However, S_g and NIMGU are not equivalent because S_g includes the effect of basal insulin on glucose uptake, whereas NIMGU does not. In addition, S_g determination via the minimal model approach seems to be controversial because it is reported to be either under- or overestimated in individuals with impaired insulin action depending on the study [21,22]. Specifically, Finegood and Tzur [23] reported that S_g between groups with significantly different insulin secretory function should be interpreted cautiously because reduced S_g in diabetic subjects is likely due to an artifact of the minimal model. In support of our data, several other studies found that S_g was significantly higher in insulin-resistant or diabetic states, interpreting this finding as a compensatory mechanism to impaired IMGU [8,24].

Glucose uptake into cells is accomplished by 2 transporter systems, namely, glucose transporters (GLUTs) and sodium-glucose cotransporters. In individuals with impaired glucose tolerance or type 2 diabetes mellitus mellitus, trafficking of the insulin-sensitive GLUT-4 transporter is decreased, possibly leading to enhanced non–insulin-mediated pathways to preserve glucose entry into the cell. This compensatory mechanism could include an increase in intrinsic activity of insulin-independent glucose mediators such as GLUT-1 and/or sodium-glucose cotransporters. Interestingly, Lopez et al recently investigated the association of IMGU and S_g in offspring of parents with type 2 diabetes mellitus (FH+) and offspring with no history of parental diabetes (FH−) [25]. They found that the positive correlation of IMGU and S_g in FH− subjects is not present in FH+ subjects, suggesting independent regulatory mechanisms of glucose uptake pathways in persons at risk for diabetes. Furthermore, they found a positive association between S_g and body mass index, which is in accordance with the strong association of NIMGU and PFAT in our data. We also included waist and thigh circumference and waist to thigh ratio, respectively, in the linear model instead of PFAT to explore a possible association of NIMGU to body fat distribution. We did not find an association of NIMGU with waist and thigh circumference or waist to thigh ratio. However, trials with more precise measurements of body fat distribution could be useful to address the role specifically of metabolically active abdominal fat. With support of the literature, our results in a large group of individuals provide further evidence of elevated NIMGU in insulin-resistant states. Therefore, NIMGU mechanisms may play an important compensatory role for plasma glucose clearance in patients with type 2 diabetes mellitus.

5. Conclusions

We found that by using a method of extrapolation to determine NIMGU, the calculated value in individuals with NGR was identical to that determined in previous studies using somatostatin-induced insulinopenia. Non–insulin-mediated glucose uptake was increased in individuals with type 2 diabetes mellitus and was related to PFAT. Furthermore, NIMGU was an independent predictor of EE. These results indicate that increasing adiposity and associated insulin resistance result in up-regulation of insulin-independent alternative pathways of glucose uptake potentially as a compensatory measure to ensure sufficient glucose flux into the cell.

Acknowledgment

We thank all study volunteers for their contribution to this study. We also thank the staff of the Clinical Research Unit on the fifth floor of the Phoenix Indian Medical Center. This study was supported by the intramural research program of the National Institute of Diabetes and Digestive and Kidney Diseases.

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