Glucose transporter 4 (GLUT4) distribution on metabolic healthy obese (MHO) vs metabolic unhealthy obese (MUO)

Juan Antonio Suárez-Cuenca (✉ suarej05@gmail.com)

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Karla Guadalupe Carvajal-Aguilera

Laboratorio de Nutrición Experimental, Instituto Nacional de Pediatría Mexico City, PO 04530, Mexico.

Luz del Carmen Camacho-Castillo

Laboratorio de Nutrición Experimental, Instituto Nacional de Pediatría Mexico City, PO 04530, Mexico.

Karen De la Vega-Moreno

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Christopher Bryan Romero-Hernández

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Eduardo Vera-Gómez

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Alejandro Hernández-Patricio

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Gabriela Alexandra Domínguez-Pérez

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100, Mexico.

Juan Ariel Gutiérrez-Buendía

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional "20 de Noviembre", ISSSTE. Mexico City, PO 03100,

Mexico.

Luis Montiel-López

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Ángel Alfonso Garduño-Pérez

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Rebeca Pérez-Cabeza de Vaca

Coordination of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Moisés Salamanca-García

Pathology Department, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03104, Mexico.

Jesús Montoya-Ramírez

Bariatric Surgery Department, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03104, Mexico.

Moisés Ortiz-Fernández

Bariatric Surgery Department, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03104, Mexico.

Omar Felipe Gaytán-Fuentes

Bariatric Surgery Department, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03104, Mexico.

Silvia García

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Sofía Lizeth Alcaráz-Estrada

Laboratorio de Medicina Genómica, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03104, Mexico.

Alberto Melchor-López

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Juan Antonio Pineda-Juárez

Coordination of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Mónica Escamilla-Tilch

Coordination of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

José Gutiérrez-Salinas

Laboratory of Experimental Metabolism and Clinical Research, Department of Clinical Research, Division of Research, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

Paul Mondragón-Terán

Tissue Engineering & Regenerative Medicine Research Group, Centro Médico Nacional “20 de Noviembre”, ISSSTE. Mexico City, PO 03100, Mexico.

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Abstract

Background. Adipose tissue is a key factor during metabolic dysregulation, whereas adipose tissue dysfunction is promoted if enlarged adipocytes, impaired adipocyte differentiation, inflammation, remodeling and/or fibrosis. As evidenced by *in vitro* studies and animal models, adipocyte hypertrophy alone is sufficient to impair glucose uptake, probably explained by changes of cell distribution of Glucose Transporter 4 (GLUT4) and trafficking, reflecting a new potential regulatory pathway. Patients with obesity can be subclassified into cardiometabolic risk phenotypes, with significant difference in adipose tissue characteristics and glucose uptake. Therefore, GLUT4 distribution in adipocytes from the so known: 1) metabolic healthy obese (MHO) and 2) metabolic unhealthy obese (MUO), may help to understand cardiometabolic risk differences between them.

Objectives. To analyze GLUT4 distribution in adipocytes from MHO vs MUO phenotypes.

Subjects and Methods. Cross-sectional observational study. Patients programmed for bariatric surgery were included. Patients were classified as MHO or MUO according to NCEP-ATPIII criteria. Samples from subcutaneous (SAT) and visceral adipose tissue (VAT) were obtained during bariatric surgery. GLUT4 expression and distribution in adipocytes were evaluated by immunofluorescence and image analysis.

Results. GLUT4 molecules showed a lower number and more spared distribution in adipocytes from MUO phenotype. Likewise, GLUT4 distribution was related to insulin resistance in both metabolic phenotypes, with differences between VAT and SAT.

Conclusion. GLUT4 expression pattern in adipocytes was related with the type of adipose tissue, the cardiometabolic risk and insulin resistance, suggesting potential and specific regulatory role.

Introduction

Obesity is a multifactorial disease involving social, economic, genetic, microbiome and individual behavior differences; along with higher risk to develop diabetes mellitus, cardiometabolic risk, obstructive sleep apnea-hypopnea syndrome, non-alcoholic fatty liver disease and certain types of cancer. It is the fifth leading cause of death, accounting for 3.4 million deaths each year [1–3]. The population with obesity can be divided according to the cumulative number of dysmetabolic components, being “metabolically healthy obese (MHO)”, those characterized by a mild increase in cardiometabolic risk, but not significantly different from normal-weight population; and “metabolically unhealthy obese (MUO)”, characterized by a significantly increased cardiometabolic risk [3–5].

In the other hand, insulin resistance is associated with clusters of metabolic and cardiovascular disorders. Qualitative and/or quantitative lipid disorders promote dysregulation pathways in adipose tissue, liver, heart, muscle and pancreas; leading to an impaired glucose metabolism. It is well recognized that adipose tissue is a highly active metabolic and endocrine organ that plays a key role in insulin resistance and metabolic syndrome. Glucose Transporter 4 (GLUT4) is an insulin-dependent transporter located in

adipocytes; whereas abnormalities in GLUT4 trafficking and intracellular translocation may promote insulin resistance [5–9].

Several murine models have described that adipocyte’s morphology is able to predict a low degree of chronic inflammation and insulin resistance; suggesting that adipocyte size plays a key role during insulin resistance development [10–12] and also hypothesize subsequent effects on GLUT4 trafficking and distribution, as well as actin structures impairment [13–16]. Our study aimed exploring whether GLUT4 number and/or distribution in different sized adipocytes may impact cardiometabolic phenotype and insulin resistance.

Results

Ten patients with morbid obesity, mean BMI 48 kg/m², mean aged 46 years old and no particular sex prevalence constituted the study population.

Then, patients were divided according to their metabolic risk phenotype (MHO n = 5 and MUO n = 5). MUO group showed higher diastolic blood pressure (Table 1) and a biochemical profile of increased plasma fasting glucose, HOMA-IR and decreased HDLc (Table 2).

Table 1
Baseline Clinical-Demographical Data (n = 10)

	MHO (n = 5)	MUO (n = 5)	p-value
Age (years old)	46.26 ± 1.5	45.66 ± 1.1	NS
Female n (%)	2(40%)	3(60%)	NS
Weight (kg)	138.2 ± 35.24	121.6 ± 25.51	NS
Height (m)	1.68 ± 1.20	1.61 ± 1.08	NS
BMI (kg/m ²)	48.27 ± 7.23	47.01 ± 10.9	NS
Waist Circumference (cm)	135.3 ± 10.41	127.6 ± 9.22	NS
Systolic blood pressure (mmHg)	117.5 ± 7.58	129.4 ± 17.82	NS
Diastolic blood pressure (mmHg)	71.67 ± 7.52	83.75 ± 10.61	0.03
Continuous variables are presented as mean ± SD, and categorical variables as n(%). Abbreviations: BMI, body mass index; Hb _{A1c} , glycated hemoglobin; LDLc, Low density lipoproteins cholesterol; HDLc, High density lipoproteins cholesterol; TNFα, Tumor necrosis factor α.			

Table 2
Cardiometabolic Profile

	MHO (n = 5)	MUO (n = 5)	p-value
PFG (mg/dL)	93.83 ± 4.95	110.4 ± 13.81	0.01
Hb _{A1c} (%)	5.73 ± 0.42	6.17 ± 0.62	NS
Insulin (mUI/mL))	17.36 ± 7.79	24.19 ± 5.96	NS
HOMA-IR	4.691 ± 2.49	7.06 ± 1.54	0.04
Total Cholesterol (mg/dL)	193 ± 36.8	164.5 ± 31.91	NS
HDLc (mg/dL)	59.46 ± 14.39	42.42 ± 9.15	0.01
LDLc (mg/dL)	104.9 ± 32.53	92.65 ± 24.59	NS
Tryglicerides (mg/dL)	143.2 ± 44.22	176.7 ± 92.28	NS
TNFα (pg/mL)	53.94 ± 61.35	41.64 ± 28.78	NS
Resistin (pg/mL)	14.11 ± 2.161	19.69 ± 8.53	NS
Adiponectin (pg/mL)	74.55 ± 68.72	74.55 ± 68.72	NS
VAT	2009	2077	NS
SAT	2418	2579	NS
Continuous variables are presented as mean ± SD, and categorical variables as n(%). Abbreviations: BMI, body mass index; Hb _{A1c} , glycated hemoglobin; LDLc, Low density lipoproteins cholesterol; HDLc, High density lipoproteins cholesterol; TNFα, Tumor necrosis factor α.			

The analysis of the pattern of distribution of GLUT-4 expressed in adipocyte membranes, evidenced a lower amount of GLUT-4 molecules and more spared distributed in MUO phenotype compared with MHO phenotype (Fig. 1).

Moreover, the amount of GLUT-4 and the distance between them (inter-GLUT distance) were negatively and positively related with HOMA-IR, respectively; whereas no significant difference was observed between metabolic risk phenotypes (Fig. 2).

Finally, inter-GLUT distance was larger in VAT, particularly in MHO phenotype (Fig. 3).

Discussion

The main finding of the present study was that the amount and distribution of GLUT4 were related with insulin resistance, and further differentiation between cardiometabolic risk profiles.

Despite the small sample size of the study population, main demographic characteristics were homogeneously distributed, whereas cardiometabolic risk were different between MHO and MUO, therefore they are comparable to other studies.

The relation between GLUT4 distribution in adipocyte's membrane with insulin resistance is consistent with initial observations in murine model, where enlarged lipid droplets and adipocyte hypertrophy were able to impair insulin sensitivity rather than inflammation alone [12]; likewise, adipocyte's size has been positively related with cardiometabolic risk factors and endothelial dysfunction [16–18]. Possible explaining mechanisms include: 1) adipocyte size affects cortical actin structures and GLUT4 trafficking vesicles, therefore influencing processes regulating insulin sensitivity; 2) higher sized adipocytes may promote to keep adipocytes away from vasculature structures, then increasing hypoxia mediated changes, and secretion of pro-inflammatory adipokines [19, 20].

In addition, GLUT4 distribution was further affected by the adipose tissue source. GLUT4 was less dense in adipocytes from VAT, which was associated with insulin resistance. However, this effect was observed in the MHO phenotype, but not in the MUO phenotype, suggesting that this lack of effect may be related to the dysfunction of the adipose tissue observed in MUO phenotype [4, 21].

Our findings propose new pathophysiological mechanism linking adipocyte size with insulin resistance, as well as potential diagnostic and therapeutic targets according to cardio-metabolic risk profiles. Some limitations of the present study were related to the small sample size and consequent potential for bias; as well as the interpretation limitation from a cross-sectional study design.

In conclusion, GLUT4 molecules were lower and more spared in adipocytes from MUO phenotype, which was related with insulin resistance markers; with an additional potential role of the source of the adipose tissue. These findings suggest a key role of GLUT4 in the pathophysiology of adipocyte-derived cardiometabolic risk.

Methods

Design and study population

Cross-sectional study evaluating the role of adipocyte's expression of GLUT-4 in insulin resistance and cardiometabolic risk factors. We enrolled patients older than 18 years old, candidate for bariatric surgery (Body Mass Index [BMI] higher than 40 kg/m² or BMI higher than 35 kg/m² experiencing obesity-related health conditions, such as t2DM, hypertension or obstructive sleep apnea/hypopnea), attended between January 2016 and December 2017 at National Medical Center “20 de Noviembre”, ISSSTE at Mexico City. Patients did not received weight-reducing therapy during 6 months previous to the enrollment and they were excluded in case of second bariatric surgery, the existence of inflammatory diseases, severe renal and/or hepatic disease, active malignancy, pregnancy or evidence of history of cardiovascular disease, considered if self-reported or diagnostic evidence of ischemic heart disease, coronary artery disease,

myocardial structural abnormalities, cardiac interventions or being under treatment for any of such conditions.

Subjects were further divided according to the cumulative number of dysmetabolic components, as “metabolically healthy obese” (MHO) or “metabolically unhealthy obese” (MUO) subjects. The former group met less than 3 of the following criteria: 1) Fasting plasma glucose above 100 mg/dl; 2) Plasma triglyceride level $\geq$ 150 mg/dl; 3) Plasma high-density lipoprotein (HDL) level for women $\leq$ 50 mg/dl, or for men $\leq$ 40 mg/dl; 4) Blood pressure $\geq$ 130/85 mmHg and 5) Waist circumference for women $>$ 88 cm, for men $>$ 102 cm; whereas MUO subjects met $\geq$ 3 criteria [22]. The study was designed and performed according to ethical guidelines of the 1975 Declaration of Helsinki and approved by the Local Committees of Research, Ethics in Research and Biosafety of the National Medical Center ‘20 de Noviembre’ ISSSTE, Mexico City. All participants provided written informed consent.

Clinical-Demographic Data

Most clinical-demographic data were obtained from a direct interview performed by experienced physicians. BMI was calculated as weight/height² [23]. Waist circumference was measured halfway between the lowest rib margin and the iliac crest at the end of a normal expiration. Blood pressure was obtained while the patient was in a seated position and was considered as the mean of three readings obtained 5 min apart using an aneroid sphygmomanometer (Welch Allyn Inc.; Skaneateles Falls, NY, USA).

Clinical Biochemistry

After a 12 h starvation, venous blood samples (4 mL) were collected into BD Vacutainer tubes (Becton, Dickinson & Co., Franklin Lakes, NJ, USA) containing EDTA, and centrifuged at 1500g, 10 min, at 4°C, separated into fractions and stored at -80°C prior to analyses. Plasma levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), glycosylated hemoglobin (Hb_{A1c}) and glucose were determined using routine clinical laboratory auto-analyser (Synchron CX9 PRO Clinical System; Beckman Coulter, Brea, CA, USA). HOMA-IR was calculated as follows: (Glucose [mg/dL] $\times$ Insulin)/405 [24].

Adipose Tissue Analyses

During the bariatric surgery, samples of 2cm³ of abdominal Subcutaneous Adipose Tissue (SAT) and Visceral Adipose Tissue (VAT) from the omentum, were obtained, and preserved.

For GLUT4 analysis, immunofluorescence assay was performed. Tissues were stained with primary antibody (GLUT4 Monoclonal Antibody (1F8). Thermo Fisher Scientific, cat No. MA1-83191) conjugated with antibody linked to a fluorophore (Goat anti-Mouse IgG (H + L) Secondary Antibody, FITC. Thermo Fisher Scientific Cat. No. 62-6511); and further added with mounting medium containing DAPI for nuclear counterstaining. Images were captured with fluorescence confocal microscope, and image analyses

(inter-GLUT4 spare distance and GLUT4 density of fluorescence) were performed with Image pro-plus software.

Statistical analysis

Clinical and biochemical quantitative data were described as mean and standard deviation, whereas qualitative data were resumed as n (%). For inferential analysis, two-tailed, U-Mann Whitney or T-test were applied according to normality of data distribution. Finally, Pearson correlation coefficient was used to evaluate the relationship between GLUT4 distribution pattern and insulin resistance markers. All statistics were performed using GraphPad Prism software (v.7). Statistical significance was considered as $p < 0.05$.

Declarations

Data availability

The datasets generated and analyzed during the current study are not publicly available due to privacy policies of the hospital and patients information; but are available from the corresponding author on reasonable request.

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Author contributions statement

J.A.S-C., K.G.C-A., L.C.C-C., and K.D-M. conceived the design and experiments. C.B.R-H., E.V-G., A.H-P., G.A.D-P., J.A.G-B., L.M-L., M.S-G., J.M-R., M.O-F., O.F.G-F., and A.A.G-P., collected data and analyzed the results. R.P-CV., S.L.A-E., A.M-L., and J.A.P-J., performed the experiments. S.G., M.E-T., J.G-S., and P.M-T critically revised the manuscript. All authors reviewed the manuscript.

Competing Interests

The author(s) declare no competing interests.

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Figures

Figure 1

GLUT-4 distribution in adipocytes and metabolic phenotype. **A.** GLUT-4 positivity signal at immunofluorescence assay in visceral adipose tissue from MHO vs MUO. Red arrow points to expression of GLUT-4 observed by this method. **B.** Representation of measures between GLUT-4 positivity distances. **C.** Quantification of immunopositivity. (*) $p < 0.05$. MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; SAT, subcutaneous adipose tissue; VAT, Visceral adipose tissue.

Figure 2

Distribution of GLUT4 and insulin resistance. Correlations between indicators of GLUT4 distribution (inter-GLUT4 spare distance and mean number of GLUT4/field (N-GLUT)) with HOMA. The relation between insulin with HOMA is also shown for comparison.

GLUT4 DISTRIBUTION

Figure 3

InterGLUT4 spare distance according to adipose tissue source and cardiometabolic phenotype.