

The insulin-sensitizing effect of rosiglitazone in type 2 diabetes mellitus patients does not require improved in vivo muscle mitochondrial function.

Citation for published version (APA):

Schrauwen-Hinderling, V., Mensink, M., Hesselink, M. K., Sels, J. P., Kooi, M. E., & Schrauwen, P. (2008). The insulin-sensitizing effect of rosiglitazone in type 2 diabetes mellitus patients does not require improved in vivo muscle mitochondrial function. *Journal of Clinical Endocrinology & Metabolism*, 93(7), 2917-2921. <https://doi.org/10.1210/jc.2008-0267>

Document status and date:

Published: 01/01/2008

DOI:

[10.1210/jc.2008-0267](https://doi.org/10.1210/jc.2008-0267)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 17 Apr. 2024

The Insulin-Sensitizing Effect of Rosiglitazone in Type 2 Diabetes Mellitus Patients Does Not Require Improved *in Vivo* Muscle Mitochondrial Function

Vera B. Schrauwen-Hinderling, Marco Mensink, Matthijs K. C. Hesselink, Jean-Pierre Sels, M. Eline Kooi, and Patrick Schrauwen

Departments of Radiology (V.B.S.-H., M.E.K.) and Internal Medicine (J.-P.S.), Maastricht University Hospital, NL-6202 AZ Maastricht, The Netherlands; and Nutrition and Toxicology Research Institute Maastricht (V.B.S.-H., M.M., M.K.C.H., P.S.), and Departments of Human Biology (M.M., P.S.) and Human Movement Sciences (M.K.C.H.), Maastricht University, 6200 MD Maastricht, The Netherlands

Aims: Our objective was to investigate whether improved *in vivo* mitochondrial function in skeletal muscle and intramyocellular lipids (IMCLs) contribute to the insulin-sensitizing effect of rosiglitazone.

Methods: Eight overweight type 2 diabetic patients (body mass index = 29.3 ± 1.1 kg/m²) were treated with rosiglitazone for 8 wk. Before and after treatment, insulin sensitivity was determined by a hyperinsulinemic euglycemic clamp. Muscular mitochondrial function (half-time of phosphocreatine recovery after exercise) and IMCL content were measured by magnetic resonance spectroscopy.

Results: Insulin sensitivity improved after rosiglitazone (glucose infusion rate: 19.9 ± 2.8 to 24.8 ± 2.1 μ mol/kg-min; $P < 0.05$). *In vivo* mitochondrial function (phosphocreatine recovery half-time: 23.8 ± 3.5 to 20.0 ± 1.7 sec; $P = 0.23$) and IMCL content ($0.93 \pm 0.18\%$ to $1.37 \pm 0.40\%$; $P = 0.34$) did not change. Interestingly, the changes in PCr half-time correlated/tended to correlate with changes in fasting insulin ($R^2 = 0.50$; $P = 0.05$) and glucose ($R^2 = 0.43$; $P = 0.08$) levels. Changes in PCr half-time did not correlate with changes in glucose infusion rate ($R^2 = 0.08$; $P = 0.49$).

Conclusion: The rosiglitazone-enhanced insulin sensitivity does not require improved muscular mitochondrial function. (*J Clin Endocrinol Metab* 93: 2917–2921, 2008)

In recent years, mitochondrial dysfunction has been implicated in the etiology of type 2 diabetes mellitus. The initial finding that a cluster of oxidative genes under control of peroxisome-proliferator activated receptor- γ (PPAR γ) coactivator-1 α (PGC-1 α) is reduced in the (pre-) diabetic state (1, 2) was rapidly followed by the demonstration of impaired skeletal muscle mitochondrial function in insulin resistance using noninvasive phosphorous magnetic resonance spectroscopy (³¹P-MRS) (3–6).

One intervention that improves insulin sensitivity in type 2 diabetes patients is the treatment with insulin-sensitizing thiazolidinediones (TZDs), which belong to the class of PPAR γ agonists. Interestingly, recent studies revealed that TZDs can cause

significant improvements in mitochondrial function in adipose tissue of both animals and humans (7–9). Rosiglitazone up-regulated a set of genes encoding mitochondrial proteins, including PGC-1 α , accompanied by an increase in mitochondrial mass and changes in mitochondrial structure in cultured adipocytes (8). We recently reported that rosiglitazone is also able to restore PGC-1 α mRNA levels in skeletal muscle of type 2 diabetic patients (10). Together, these findings suggest that the insulin-sensitizing effect of rosiglitazone could be due to an improvement in *in vivo* mitochondrial function in skeletal muscle. Therefore, we investigated if: 1) an improvement of mitochondrial function underlies the TZD-induced improvement in insulin sensitivity, and 2) such an effect is mediated by reducing skeletal muscle lipid

0021-972X/08/\$15.00/0

Printed in U.S.A.

Copyright © 2008 by The Endocrine Society

doi: 10.1210/jc.2008-0267 Received February 5, 2008. Accepted April 29, 2008.

First Published Online May 6, 2008

Abbreviations: FFA, Unesterified free fatty acid; GIR, glucose infusion rate; IMCL, intramyocellular lipid; MRS, magnetic resonance spectroscopy; PGC-1 α , peroxisome-proliferator activated receptor- γ coactivator-1 α ; ³¹P-MRS, phosphorous magnetic resonance spectroscopy; PPAR γ , peroxisome-proliferator activated receptor- γ ; TZD, thiazolidinedione.

content. Hence, we investigated insulin sensitivity and *in vivo* skeletal muscle mitochondrial function using ^{31}P -MRS together with intramyocellular lipid (IMCL) content using proton magnetic resonance spectroscopy in type 2 diabetic patients before and after 8-wk treatment with rosiglitazone.

Subjects and Methods

Subjects

Eight male overweight patients with type 2 diabetes mellitus participated in this study. Subjects were on oral antidiabetic medication (metformin or sulfonylureas-derivatives) and had no major health problems besides their diabetes. The protocol was approved by the institutional Medical Ethics Committee, and every subject signed an informed consent after procedures had been explained.

Study design

Fourteen days before the experimental trial, any prior antidiabetic medication was discontinued. Subjects were asked not to participate in (exhaustive) physical activity the last 3 d preceding the measurements and to consume a diet according to the Dutch guidelines for a healthy diet. After baseline measurements of *in vivo* mitochondrial function, IMCL content, insulin sensitivity, and plasma concentrations of glucose and insulin, subjects received rosiglitazone (2×4 mg/d) during 8 wk. All measurements were repeated after the treatment. During the treatment, subjects visited the laboratory every 2 wk for measurements of fasting glucose and to check compliance.

Hyperinsulinemic euglycemic clamp

After an overnight fast, insulin sensitivity was measured with a 3-h hyperinsulinemic euglycemic clamp as reported earlier (10). The rate at which glucose was infused during the last 30 min of the clamp to maintain euglycemia [glucose infusion rate (GIR)] was used as a measure of whole body insulin sensitivity.

Magnetic resonance spectroscopy (MRS)

MRS measurements were performed at 1.5 T (Intera; Philips Medical Systems, Best, The Netherlands).

In vivo mitochondrial function by ^{31}P -MRS

In vivo mitochondrial function was investigated by ^{31}P -MRS (6-cm surface coil, free induction decay, repetition time = 4 sec, $n = 1$) by assessing phosphocreatine recovery half-time of the mono-exponentially fitted time course after knee-extension exercise in the vastus lateralis muscle as reported earlier (5).

IMCL by ^1H -MRS imaging

Image-guided ^1H -MRS imaging (20×20 voxels, field of view = 10 cm, point resolved spectroscopy, repetition time = 1500 msec, spin echo pulse sequences = 24 msec) was performed in the vastus lateralis muscle as reported earlier (5) and fitted with Java-based magnetic resonance user interface (11).

Because of insufficient spectral quality in one case, the IMCL values of only seven subjects are reported.

Blood analyses

Blood was collected in EDTA-containing tubes, and plasma was frozen in liquid nitrogen and stored at -80 C until assayed. Plasma unesterified free fatty acid (FFA) and glucose were measured with enzymatic assays automated on a Cobas Fara/Mira (FFA: Wako Nefa C test kit; Wako Chemicals, Neuss, Germany; glucose: hexokinase method, La-Roche, Basel, Switzerland). Insulin concentration was determined using a RIA (LINCO Research, Inc., St. Charles, MO).

Statistics

Results are reported as mean \pm SEM and considered significant if $P < 0.05$. The effect of rosiglitazone on selected parameters was determined by a two-sided paired Student's *t* test. To evaluate the relationship between variables, Pearson correlation coefficients were calculated (SPSS for Windows 11.5 software; SPSS, Inc., Chicago, IL).

Results

Subject characteristics

Subject characteristics before and after 8-wk rosiglitazone treatment are shown in Table 1.

Insulin sensitivity and substrate oxidation

Whole body insulin sensitivity (GIR) significantly improved after 8-wk rosiglitazone treatment (from 19.9 ± 2.8 to 24.8 ± 2.1 $\mu\text{mol}/\text{kg}\cdot\text{min}$; $P = 0.04$). Basal and insulin-stimulated glucose and lipid oxidation were not affected by 8-wk rosiglitazone treatment. However, the increase in respiratory quotient upon insulin stimulation was more pronounced after rosiglitazone, suggesting improved metabolic flexibility (before: from 0.82 ± 0.01 to 0.87 ± 0.02 ; after: from 0.79 ± 0.01 to 0.88 ± 0.01 ; $P = 0.06$).

IMCL content

IMCL content was unchanged after rosiglitazone ($0.69 \pm 0.14\%$ before treatment and $1.01 \pm 0.29\%$ after treatment; $P = 0.35$). IMCL content did not correlate with insulin sensitivity

TABLE 1. Baseline subject characteristics

	Before	After	P value
Age (yr)	61.8 ± 1.6		
Body weight (kg)	90.2 ± 5.2	91.4 ± 5.2	NS
BMI (kg/m^2)	29.3 ± 1.1	29.7 ± 1.0	NS
$\text{VO}_{2\text{max}}$ ($\text{ml}/\text{kg}\cdot\text{min}$)	31.5 ± 2.3	ND	
Glucose (mmol/liter)	9.3 ± 0.7	8.8 ± 0.7	NS
Insulin (mU/liter)	16.1 ± 2.9	13.4 ± 1.8	NS
Free fatty acid ($\mu\text{mol}/\text{liter}$)	431 ± 30	398 ± 42	NS
Insulin sensitivity (GIR, $\mu\text{mol}/\text{kg}\cdot\text{min}$)	19.9 ± 2.8	24.8 ± 2.1	0.04

Data are mean \pm SE. BMI, Body mass index; ND, not determined; NS, not significant; $\text{VO}_{2\text{max}}$, maximum oxygen consumption.

($P = 0.87$) or *in vivo* mitochondrial function ($P = 0.27$). Changes in IMCL content did neither correlate with changes in insulin sensitivity ($P = 0.68$) nor with changes in mitochondrial function ($P = 0.49$).

In vivo mitochondrial function

During the knee-extension protocol, the PCr levels decreased initially in the vastus lateralis muscle until a steady state was reached after 2–3 min. Steady-state PCr levels were similar before and after rosiglitazone treatment (at $72.7 \pm 2.8\%$ and $70.4 \pm 3.2\%$ of the resting baseline value; $P = 0.3$). None of the subjects showed substantial acidification during the exercise protocol, with similar end-exercise pH values before and after treatment (7.11 ± 0.01 and 7.03 ± 0.03 ; $P = 0.14$).

Eight weeks of rosiglitazone treatment did not improve mitochondrial function, as reflected by an unchanged PCr recovery half-time (from 23.8 ± 3.5 to 20.0 ± 1.7 sec; $P = 0.23$). In fact, three subjects showed an improvement in mitochondrial function, reflected by a reduced PCr recovery half-time of more than 5%, whereas five subjects showed a decrease or no change (Fig. 1). However, interestingly, the changes in PCr recovery half-time correlated positively with the changes in plasma insulin levels ($R^2 = 0.50$; $P = 0.05$) and tended to correlate with changes in plasma glucose levels ($R^2 = 0.43$; $P = 0.08$) (Fig. 2). There was no correlation between the changes in PCr recovery half-time and those in insulin sensitivity ($R^2 = 0.08$; $P = 0.49$).

Discussion

A decreased mitochondrial function has been implicated in the development of insulin resistance. Based on previous results obtained in white adipose tissue showing induction of mitochondrial biogenesis (7) and in myotubes, showing increased PGC-1 α expression and insulin-stimulated glycogen synthesis (12) upon rosiglitazone treatment, we predicted that treating human type 2 diabetic patients for 8 wk with the PPAR γ agonist rosiglitazone would result in improved mitochondrial function that could underlie the improvement in insulin sensitivity. Although 8-wk rosiglitazone treatment significantly improved insulin sensitivity, we did, however, not observe

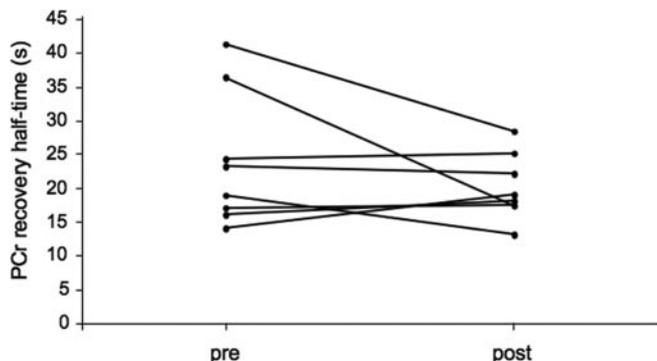


FIG. 1. Individual changes in PCr recovery half-time upon rosiglitazone treatment. post, After; pre, before; s, sec.

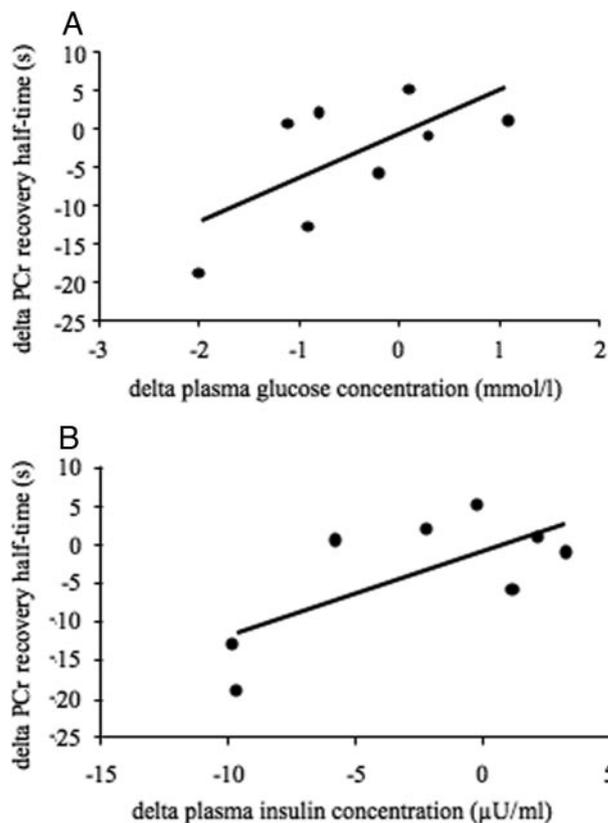


FIG. 2. A, Correlation between the change in plasma glucose levels and the change in PCr recovery half-time ($R^2 = 0.43$; $P = 0.07$). B, Correlation between the change in plasma insulin levels and the change in PCr recovery half-time ($R^2 = 0.50$; $P = 0.05$).

significantly improved mitochondrial function, as determined by postexercise PCr recovery half-time, and no change in IMCL content. Moreover, changes in insulin sensitivity did not correlate with the changes in mitochondrial function or IMCL content. Thus, the present *in vivo* study in type 2 diabetic patients shows that rosiglitazone-enhanced insulin sensitivity does not require improved muscular mitochondrial function.

The lack of effect of rosiglitazone on *in vivo* mitochondrial function was not anticipated because we previously observed that 8-wk rosiglitazone treatment up-regulated the skeletal muscle expression of PGC-1 α , and restored succinate dehydrogenase activity (10) and uncoupling protein-3 protein content (13) in type 2 diabetic patients. However, in these previous studies, we also noted that these improvements were not accompanied by changes in mitochondrial content, as assessed by measuring the protein content of five structural subunits of complexes I–V of the respiratory chain (10). The unchanged *in vivo* mitochondrial function of the current study suggests that the earlier reported increase in PGC-1 α expression and succinate dehydrogenase activity (10) do not necessarily translate into improvements in *in vivo* mitochondrial function within the time frame of the study.

How rosiglitazone improves whole body and muscular substrate metabolism and insulin sensitivity remains to be elucidated. It has been suggested that the improvement in skeletal muscle insulin sensitivity upon rosiglitazone could be an indirect

effect, mediated by metabolic changes in adipose tissue, leading among others to increased levels of adiponectin and decreased levels of FFA, which may in turn influence muscular metabolism to result in an improved insulin sensitivity (for a recent review, see Ref. 14). Indeed, it has been shown repeatedly that rosiglitazone increases plasma adiponectin levels; in fact, we observed in a similar population and intervention a 5-fold increase in adiponectin levels after 8-wk rosiglitazone treatment (from 3.3 ± 0.4 to $11.8 \pm 1.8 \mu\text{g/ml}$, $n = 11$; $P < 0.001$; unpublished observations). Although this notion of an indirect mechanism is perfectly in line with the results presented here, we cannot exclude that rosiglitazone also exerts direct effects on muscular metabolism that are involved in the improvement of muscular insulin sensitivity. However, what the present study does show is that such improvement is not mediated by an increased *in vivo* mitochondrial function.

Although rosiglitazone did not have an effect on *in vivo* mitochondrial function, the change in PCr recovery half-time did correlate with the rosiglitazone-induced decline in fasting plasma insulin and glucose levels. Thus, those subjects in which rosiglitazone decreased fasting insulin and glucose levels the most showed the most prominent improvement in mitochondrial function. This can still be compatible with rosiglitazone having a stimulating effect on mitochondrial function but may indicate that the duration of our study was too short to already detect these changes at a statistically significant level. In addition, the number of subjects in our study was low. However, it should be noted that only in three of eight subjects mitochondrial function improved more than 5%, whereas it decreased or was unaltered in the other five. However, regardless of this, rosiglitazone treatment did significantly improve insulin sensitivity. Therefore, although it cannot be excluded that rosiglitazone will on the longer term also improve mitochondrial function, such improvement is not a prerequisite for the insulin-sensitizing effect of rosiglitazone.

Alternatively, the relationship between plasma glucose/insulin and *in vivo* mitochondrial function may indicate that hyperinsulinemia and/or hyperglycemia has a negative impact on *in vivo* mitochondrial function of skeletal muscle and that a reduction in glucose/insulin levels thereby improved mitochondrial function. Support for mitochondrial dysfunction being a consequence of insulin resistance comes from a recent study by Asmann *et al.* (15), in which plasma insulin and glucose levels were artificially kept similar between type 2 diabetic patients and healthy controls. Under this condition of similar postabsorptive insulin and glucose levels, *ex vivo* skeletal muscle ATP production and mitochondrial DNA copy number were not different between control subjects and diabetic patients, but type 2 diabetic subjects had a blunted increase in mitochondrial ATP production in response to insulin. The authors concluded that the mitochondrial aberrations observed in diabetic patients can be attributed to multiple factors related to insulin action rather than resulting from intrinsic mitochondrial defects.

Consistent with the lack of effect of rosiglitazone on *in vivo* mitochondrial function, also IMCL content was unchanged after rosiglitazone treatment. This confirms earlier studies by us (10) and others (16), and these results are in line with the notion that

although IMCL content is generally correlated with insulin resistance, the IMCL content is not a direct determinant of insulin sensitivity.

In conclusion, we have shown that PCr recovery half-time was not affected by 8-wk rosiglitazone treatment in type 2 diabetic patients but that rosiglitazone did improve whole body substrate metabolism and insulin sensitivity. These changes occurred in the absence of rosiglitazone-induced changes in muscular fat content. Thus, neither an improved mitochondrial function nor the lowering of IMCL is a prerequisite for rosiglitazone-enhanced insulin sensitivity.

Acknowledgments

The Java-based magnetic resonance user interface software package was kindly provided by the participants of the European Research Network programs: Human Capital and Mobility, CHRX-CT94-0432 and Training and Mobility of Researchers, ERB-FMRX-CT970160.

Address all correspondence and requests for reprints to: Vera B. Schrauwen-Hinderling, Department of Radiology, Maastricht University Hospital, P.O. Box 5800, NL-6202 AZ Maastricht, The Netherlands. E-mail: v.schrauwen@hb.unimaas.nl.

This work was supported by a grant from GlaxoSmithKline. P.S. is supported by a fellowship of the Royal Netherlands Academy of Arts and Sciences. M.K.C.H. is supported by a VIDI Research Grant for innovative research from The Netherlands Organization for Scientific Research (Grant 917.66.359).

Disclosure Summary: V.B.S.-H., M.M., M.K.C.H., J.-P.S., and M.E.K. have nothing to declare. P.S. received a grant for this study from GlaxoSmithKline.

References

1. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ 2003 Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *Proc Natl Acad Sci USA* 100:8466–8471
2. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC 2003 PGC-1 α -responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet* 34:267–273
3. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI 2003 Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 300:1140–1142
4. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI 2004 Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 350:664–671
5. Schrauwen-Hinderling VB, Kooi ME, Hesselink MK, Jeneson JA, Backes WH, van Echteld CJ, van Engelshoven JM, Mensink M, Schrauwen P 2007 Impaired *in vivo* mitochondrial function but similar intramyocellular lipid content in patients with type 2 diabetes mellitus and BMI-matched control subjects. *Diabetologia* 50:113–120
6. Szendroedi J, Schmid AI, Chmelik M, Toth C, Brehm A, Krssak M, Nowotny P, Wolz M, Waldhausl W, Roden M 2007 Muscle mitochondrial ATP synthesis and glucose transport/phosphorylation in type 2 diabetes. *PLoS Med* 4:e154
7. Wilson-Fritch L, Burkart A, Bell G, Mendelson K, Leszyk J, Nicoloso S, Czech M, Corvera S 2003 Mitochondrial biogenesis and remodeling during adipogenesis and in response to the insulin sensitizer rosiglitazone. *Mol Cell Biol* 23:1085–1094

8. Wilson-Fritch L, Nicoloso S, Chouinard M, Lazar MA, Chui PC, Leszyk J, Straubhaar J, Czech MP, Corvera S 2004 Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone. *J Clin Invest* 114:1281–1289
9. Bogacka I, Xie H, Bray GA, Smith SR 2005 Pioglitazone induces mitochondrial biogenesis in human subcutaneous adipose tissue in vivo. *Diabetes* 54:1392–1399
10. Mensink M, Hesselink MK, Russell AP, Schaart G, Sels JP, Schrauwen P 2007 Improved skeletal muscle oxidative enzyme activity and restoration of PGC-1 α and PPAR β/Δ gene expression upon rosiglitazone treatment in obese patients with type 2 diabetes mellitus. *Int J Obes (Lond)* 31:1302–1310
11. Naressi A, Couturier C, Castang I, de Beer R, Graveron-Demilly D 2001 Java-based graphical user interface for MRUI, a software package for quantitation of in vivo/medical magnetic resonance spectroscopy signals. *Comput Biol Med* 31:269–286
12. Al-Khalili L, Forsgren M, Kannisto K, Zierath JR, Lonnqvist F, Krook A 2005 Enhanced insulin-stimulated glycogen synthesis in response to insulin, metformin or rosiglitazone is associated with increased mRNA expression of GLUT4 and peroxisomal proliferator activator receptor γ co-activator 1. *Diabetologia* 48:1173–1179
13. Schrauwen P, Mensink M, Schaart G, Moonen-Kornips E, Sels JP, Blaak EE, Russell AP, Hesselink MK 2006 Reduced skeletal muscle uncoupling protein-3 content in prediabetic subjects and type 2 diabetic patients: restoration by rosiglitazone treatment. *J Clin Endocrinol Metab* 91:1520–1525
14. Quinn CE, Hamilton PK, Lockhart CJ, McVeigh GE 2007 Thiazolidinediones: effects on insulin resistance and the cardiovascular system. *Br J Pharmacol* 153:636–645
15. Asmann YW, Stump CS, Short KR, Coenen-Schimke JM, Guo Z, Bigelow ML, Nair KS 2006 Skeletal muscle mitochondrial functions, mitochondrial DNA copy numbers, and gene transcript profiles in type 2 diabetic and nondiabetic subjects at equal levels of low or high insulin and euglycemia. *Diabetes* 55:3309–3319
16. Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enoksson S, Inzucchi SE, Shulman GI, Petersen KF 2002 The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* 51:797–802