Acute Hyperinsulinemia Differentially Regulates Interstitial and Circulating Adiponectin Oligomeric Pattern in Lean and Insulin-Resistant, Obese Individuals

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Context: Hyperinsulinemia emerges as a negative modulator of the circulating high-molecular-weight adiponectin multimers.

Objectives: Here we asked whether, in vivo, acute hyperinsulinemia regulates adiponectin formation and oligomeric complex distribution at the transcriptional or posttranslational level.

Design: Nine lean and nine uncomplicated obese males were studied in the postabsorptive state and during a euglycemic-hyperinsulinemic clamp combined with the microdialysis technique. Subcutaneous abdominal adipose tissue biopsies and interstitial and serum samples were taken at baseline and after the hyperinsulinemia. Adiponectin complexes were characterized by nonheating/nonreducing SDS-PAGE.

Results: At baseline, serum and interstitial total adiponectin levels were lower (P < 0.01) in obese than in lean subjects primarily due to a reduction of the high-molecular-weight isoforms. After hyperinsulinemia, serum and interstitial total adiponectin was reduced in both groups. The degree of adiponectin reduction was more prominent in interstitial fluid than in serum. Lean individuals showed an equal suppression of the high-, low-, and middle-molecular-weight adiponectin complexes both in serum and in situ (P < 0.01 vs. basal). In obese subjects, despite the lower interstitial adiponectin subfractions, insulin challenge reduced significantly the circulating middle-molecular-weight forms only. At the mRNA level, adiponectin and its receptors 1 and 2, as well as the abundance of the endoplasmic reticulum chaperone proteins ERp44 and Erp1-Lα were similar within the groups, before and after the clamp.

Conclusions: In human obesity, the impaired adiponectin oligomeric pattern in the circulation is mimicked at the tissue level, and hyperinsulinemia may differentially affect the compartmental distribution of the adiponectin complexes. (J Clin Endocrinol Metab 94: 4508–4516, 2009)

Hypoadiponectinemia emerges as a key feature of obesity, type 2 diabetes (T2D), and other insulin-resistance (IR) states (1–4). In humans, plasma adiponectin is composed of different oligomeric species including the trimers (low molecular weight, LMW), the albumin-binding trimers (Alb-LMW), and the hexamers (middle molecular weight, MMW) as well as the 12- or larger multimers (high molecular weight, HMW) (1, 5). Interestingly, the IR-associated adi-
Adiponectin decrease seems attributable to a selective down-regulation of the HMW multimers, whereas the lower-order isoforms are basically unaffected (2–4). The impaired adiponectin oligomeric distribution is of importance because both the insulin-sensitizing and anti-atherosclerotic activities of this adipokine are critically dependent upon the abundance of the HMW forms (4, 6, 7).

Consistent observations support the concept that adiponectin oligomerization is primarily controlled at the level of cellular secretion from adipocytes (5, 8–11). In human obesity, however, despite the disproportionate profile of the circulating adiponectin subfractions away from the HMW multimers, isolated adipocytes show an intracellular content of HMW complexes strikingly greater than that in the bloodstream (8), suggesting that a considerable amount of the higher-order adiponectin forms are retained inside the cell (8, 11, 12). It has thus been hypothesized that distinct secretory pathways may regulate the compartmental distribution of the adiponectin oligomers (13). Recent evidence points to a pair of endoplasmic reticulum (ER) resident proteins, including the ER protein of 44 kDa (ERp44) and its binding partner Ero1-Lα, as molecular chaperones involved in the maturation and release of the intracellularly sequestered HMW multimers, respectively (12, 14). On the other hand, other factors beyond the adipose secretion (e.g., molecular metabolism) may also explain the aberrant circulating adiponectin oligomeric profile in obesity (6, 15, 16).

Thus far, insulin and testosterone increasingly emerge as selective inhibitors of the circulating HMW adiponectin (2, 10, 11). However, in obese IR individuals, notwithstanding the profound alterations of testosterone concentrations (17), the impairment of adiponectin oligomeric pattern still persists in both genders, and women exhibit unexpectedly higher HMW levels than men (3, 18, 19). These findings implicate that, in obesity, chronic hyperinsulinemia or IR rather than testosterone may be major determinants of the disproportionate adiponectin compartmental distribution. Moreover, the observation that exogenous hyperinsulinemia acutely decreases the circulating HMW without affecting the mRNA abundance of adiponectin in the adipose tissue (AT) supports the concept that insulin regulation of adiponectin secretion primarily lies at the posttranscriptional level (11, 20–22). Finally, insulin has also been reported to down-regulate the expression of the adiponectin receptor 1 (AdipoR1) and 2 (AdipoR2), possibly contributing to the adiponectin sensitivity at the target tissues (23). Yet, whether insulin modulates the adipose cellular machinery at the level of local production and subsequent spillover of in situ released adiponectin complexes in humans remains largely elusive.

The microdialysis (MD) technique is a validated approach to gain access to the AT intercellular water space in vivo, yielding unique information on the molecular milieu at the tissue level (24–27).

The objectives of the present study were 1) to characterize the adiponectin oligomeric composition at the level of AT interstitial fluid in vivo; 2) to investigate whether insulin affects adiponectin formation and oligomers distribution at the transcriptional, posttranslational, and/or secretory level; and 3) to determine whether lean and obese subjects exhibit a different response to acute hyperinsulinemia.

**Subjects and Methods**

**Subjects**

Eighteen male volunteers were selected among those recruited through an advertisement in a local newspaper. The participants were enrolled into the study if they met the following criteria: 1) a healthy state, according to physical examination and screening laboratory tests; 2) absence of clinical or laboratory signs of acute inflammation; and 3) no current regular medication. The selected subjects, which have also been studied in another protocol (24), were divided into a group of lean (n = 9) and obese (n = 9) individuals.

An informed written consent was obtained from all volunteers before their participation in the study, which has been approved by the Ethical Committee of Gothenburg University and carried out according to Declaration of Helsinki principles.

**Experimental design**

The volunteers underwent two study sessions, at 2- to 3-d intervals, in the following order: 1) basal evaluation and 2) glucose clamp study. For each session, the subjects were admitted to the research center at 0800 h after an overnight fast and investigated in a temperature-controlled room (26 ± 2 C).

At the basal evaluation, a body composition analysis (dual-energy x-ray absorptiometry, DPX-IQ; Lunar Radiation, Madison, WI) and a sc abdominal AT biopsy were performed. Tissue specimens (1–2 g) were in part stored at −80 C before RNA extraction (guanidinium thiocyanate method) and also used for cell size measurement (28).

In the clamp study, the sc MD technique was combined with the euglycemic-hyperinsulinemic clamp (EHC) to evaluate the variations of adiponectin and its oligomers after acute hyperinsulinemia. The study started with placement of catheters into an antecubital vein for infusions and, retrogradely, into a wrist vein for arterial blood sampling of arterialized venous blood. After vein cannulation, the euglycemic-hyperinsulinemic clamp (EHC) was performed in the basal state and during insulin infusion. The basic principle of the MD technique has been previously described in detail (24–26). Briefly, custom-made MD linear probes (Plasmaphlo OP-02, Asahi, Japan) with a molecular mass cutoff of 3000 kDa were inserted without anesthetics into the periumbilical region of the sc abdominal fat. The membranes were perfused at a rate of 1.0 μl/min with 1% human albumin (vol/vol) in isotonic saline by a microinjection pump (CMA Microdialysis AB, Stockholm, Sweden). After insertion, a period of
approximately 60 min was allowed before starting the dialysate sampling. Previous methodological in vitro experiments as well as in vivo studies showed that, under these dialyzing conditions, stable rates of molecule exchange across the membrane were actually achieved for adiponectin and its oligomers during this time scale (data not shown). Dialysate fractions were thus collected at 60-min intervals in the basal state and during the hyperinsulinemia. The period for the collection of dialysates was paralleled by intermittent blood samplings, and the fractions were stored at −70°C until analyzed.

Insulin sensitivity was evaluated by the EHC technique (29). A primed-continuous iv insulin infusion was administered for 210 min at a constant rate of 40 mU/m²·min⁻¹. This infusion achieved a steady-state serum insulin concentration of 499.5 (429.0–530.2) and 675.0 (530.2–765.0) pmol/liter [median (25–75th percentile)] in lean and obese subjects, respectively. Plasma glucose was maintained at 5.0 mmol/liter with a variable infusion of a 20% glucose solution. The insulin-stimulated glucose disposal rate (M(S)), normalized per kilogram of body weight (M(S)kg⁻¹) or fat-free mass (M(S)fat), was calculated for the last 40-min period of the second hour of the clamp (time 120–180 min), which defined the hyperinsulinemic steady state.

Finally, at 210 min during the clamp, a biopsy from the sc abdominal fat was taken for the gene profile evaluation after hyperinsulinemia.

**Determination of adiponectin oligomers**

The adiponectin oligomers in serum and AT interstitial fluid were separated by SDS-PAGE under nonheating and nonreducing conditions, as described (30). Briefly, samples were initially diluted 10-fold with deionized water and mixed with nonreducing sample buffer. We separated 2 µl of the diluted samples plus 2 µl protein loading buffer under nondenaturing conditions by NuPAGE 3–8% Tris-acetate precast gels (Invitrogen, Carlsbad, CA). Each gel was calibrated against standards of recombinant human adiponectin (HEK293; Bio-Vendor, LLC, Candler, NC), a native molecule with 100% homology with the human serum counterpart, and the quantity of a particular gene was normalized to that of 18s rRNA (32).

In each subject, oligomer distribution and absolute adiponecin concentration were quantified in the same serum and dialysate samples. The proportion of adiponectin oligomers as a function of total protein was calculated by dividing band densitometry of each oligomer by total density in each lane. Moreover, the total adiponecin concentration was measured by an ultrasensitive ELISA (B-Bridge, Sunnyvale, CA; intra- and inter-

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central body fat distribution and increased fat-free mass values. Moreover, obese subjects exhibited larger adipocyte cell size and lower testosterone levels than lean counterparts. Finally, the increased fasting serum insulin, along with the reduced $M_s$, showed the IR in these obese individuals.

Adiponectin oligomeric distribution in serum and interstitial fluid

In the basal state, total interstitial ($P = 0.01$) and serum ($P < 0.01$) adiponectin levels were higher in lean than in obese. These differences were attributable to a lower concentration of the HMW multimers in obese than in lean, either in interstitial fluid ($P < 0.05$) or in the circulation ($P < 0.01$). In contrast, the basal interstitial and serum levels of LMW and MMW forms did not differ across the groups (Figs. 2 and 3, A–D).

After hyperinsulinemia, interstitial and serum total adiponectin concentrations decreased ($P < 0.01$ vs. basal) in either group. In general, the reduction of interstitial adiponectin was more prominent in serum than in interstitial fluid. Interestingly, in lean subjects, the decline of each adiponectin fraction in dialysate was paralleled by a significant decrement also in serum. Accordingly, after hyperinsulinemia, obese subjects exhibited a significant suppression ($P < 0.01$ vs. basal) of the three interstitial adiponectin complexes. In obese individuals, however, insulin challenge reduced significantly ($P = 0.01$ vs. basal) the serum MMW forms only, whereas no significant variations of the circulating HMW and trimeric adiponectin levels were seen (Figs. 2 and 3, A–D).

Altogether, these data suggest that, in the postabsorptive state, the obesity-linked impairment of adiponectin oligomeric pattern in serum is mimicked at the tissue level and acute hyperinsulinemia may differentially regulate the distribution of the circulating adiponectin fractions in lean and obese individuals.

Adipose gene profile

To further examine the short-term regulation of adiponectin secretion by insulin, we characterized the gene expression profile in the sc abdominal AT (Table 2).

At baseline, the mRNA abundance of adiponectin and its putative receptors, the AdipoR1/2, was not significantly different between the groups. After the hyperinsulinemia, neither adiponectin nor AdipoR1 gene changed significantly, whereas AdipoR2 expression tended to increase in lean. In both groups, we found abundant, but similar, mRNA levels of ERp44 and Ero1-La either at baseline or after the clamp. Notably, the basal gene expression of GLUT4 was reduced in obese, and insulin challenge increased significantly the GLUT4 mRNA levels in lean individuals only. Collectively, these findings indicate that the effects of insulin on circulating adiponectin concentrations are not reflected at the transcriptional level, and GLUT4 and AdipoR2 induction appears to be resistant to insulin in obesity.

For all subjects, the adipocyte cell size correlated negatively with $M_{bw}$ ($r_p = -0.712; P < 0.01$) and GLUT4 mRNA levels ($r_p = -0.636; P < 0.01$). After adjusting for total fat mass, cell size, fasting insulin, and testosterone levels, the basal gene expression of adiponectin, AdipoR2, GLUT4, ERp44, and Ero1-La were tightly associated (supplemental Table 1, published as supplemental data on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

Adiponectin isoforms, adiposity, and insulin sensitivity

In the combined group, both serum and interstitial total as well as HMW adiponectin basal levels were negatively associated with measures of body fat, central fat mass distribution, and adipocyte diameter, whereas a positive correlation with $M_s$ was seen (data not shown). Multiple regression analysis revealed that after adjusting for total body fat, waist-
to-hip ratio, and testosterone, adipose cell size and Mbw were independent determinants of basal serum ($R^2 = 0.297$ and 0.323; $P < 0.05$) and interstitial ($R^2 = 0.371$ and 0.210; $P < 0.05$) HMW adiponectin, respectively. Remarkably, we observed a positive correlation between basal total and each of the three adiponectin isoforms both in serum and AT interstitial fluid (supplemental Table 2). Also, a strong correlation between HMW and total adiponectin concentrations either in serum or in dialysate was found (Fig. 4, A–D), and this persisted after controlling for the confounding effect of total fat mass, adipose cell size, testosterone, and Mbw. These findings favor the idea that obesity-linked down-regulation of HMW adiponectin appears more closely explained by the degree of IR rather than by fat mass expansion or testosterone, and HMW and total adiponectin may be regulated synchronously at the level of cellular production.

Discussion

The present in vivo study describes, for the first time, the oligomeric adiponectin distribution at the cellular level and in the bloodstream in lean and IR, obese individuals. The results demonstrate that, either in situ or in the circulation, the HMW form represents the predominant secretory product, which appears selectively down-regulated in obesity. Importantly, we show that acute hyperinsulinemia may differentially affect the compartmental distribution of adiponectin complexes in serum and AT intercellular water space. Finally, our findings support the concept that the secretion of HMW and total adiponectin may be regulated synchronously.

Mounting evidence implicates a close relationship between the selective deficiency of the HMW adiponectin and the development of T2D or, to a lesser extent, cardiovascular events (4, 5). The molecular stability and the lack of interconversion of adiponectin complexes in the bloodstream (8, 31) highlight the importance of the adipocyte secretory pathway in determining the circulating pattern of adiponectin isoforms. As yet, it has not been clear whether, in vivo, all forms of adiponectin are secreted by adipocytes or to what extent the adiponectin fractions released in situ are delivered into the circulation.

A key finding of the present study was that in the postabsorptive state, the pattern of circulating adiponectin oligomers was mimicked at the interstitial level both in lean and obese subjects. Notably, either in situ or in the bloodstream, the HMW multimer was the main secretory product, and the selective down-regulation of HMW explained the obesity-linked hypoadiponectinemia. Despite these variations, we failed to find significant group differences in basal adiponectin gene expression, implicating an important regulation of adiponectin secretion at the posttranscriptional level. However, although adiposity or IR may also be accompanied by a down-regulated mRNA expression of adiponectin in the AT (15, 20, 34–36), in human obesity, the intracellular content of HMW multimers did not appear to be low (8), and a significant portion of de novo-synthesized molecules is known to be sequestered within the adipocyte (12). Based on these assumptions, it is possible to speculate that the selective decrement of interstitial HMW we found in obese subjects was likely due to an altered compartmentalization between the HMW complexes retained within, or in situ released by, the enlarged and IR fat cell. The inverse correlation between interstitial HMW and adipocyte cell size, along with the observation that adipocyte size and glucose

![Image](https://academic.oup.com/jcem/article-abstract/94/11/4508/2596994/4512)
disposal rate were independent predictors of both interstitial and serum basal HMW levels, may well support such a hypothesis. Thus, in obesity, adipocyte enlargement and/or IR, rather than fat mass expansion or testosterone levels, appear to be prerequisites for the impaired cellular secretion of the HMW complexes.

The cellular retention and release of HMW adiponectin are controlled by ERp44 and Ero1-Lα, critical chaperones up-regulated by thiazolidinediones, drugs that preferentially stimulate the secretion of HMW (12, 14). Down-regulation of these chaperones may be thus predicted to negatively impact the release of the multimeric fractions. It is not apparent from our data that the gene expression of these molecules differed across the groups, and the protein levels of these mediators appear to generally match their mRNA abundance (12). However, we cannot rule out that a different cellular activity of these chaperons may impair the efficiency of the adipocyte secretory machine. The correlation between the ERp44, Ero1-Lα, and adiponectin genes reasonably indicates that these chaperones are coregulated with adiponectin during adipocyte differentiation, providing a mechanism by which mature adipose cells may differentiate an assembly/secretion competent from a degradation-prone pool of adiponectin, respectively (12).

So far, compelling circumstantial data indicate that hyperinsulinemia can trigger a selective reduction of the circulating HMW adiponectin (2, 3, 8, 12). However, in T2D as well as among obese, IR individuals, short-term insulin administration may also exert an inhibitory effect on the trimeric forms (2, 9), the significance of which is not well appreciated. Interestingly, the Alb-LMW form was hypothesized to influence the formation, functional activities, and degradation of the adiponectin multimers (1). Moreover, although a physiological insulinemia is required to maintain adiponectin expression in mature adipocytes (37), chronic hyperinsulinemia, a common hallmark of the obese and IR state (38), may induce a dysregulated adiponectin oligomerization. Yet, the mechanism by which insulin governs the adiponectin oligomers production, release, and compartmental distribution in vivo has not been fully elucidated.

Here, we show that an acute hyperinsulinemia broadly within physiological ranges decreased the total adiponectin levels, and the degree of reduction was

![Graph](https://example.com/graph.png)

**FIG. 3.** Serum (s) levels of total (A), HMW (B), MMW (C), and LMW (D) adiponectin in lean and obese individuals at baseline (open boxes) and after the EHC (filled boxes). *, P < 0.01 obese vs. lean; †, P < 0.01 EHC vs. basal; ‡, P = 0.01 EHC vs. basal; §, P < 0.05 EHC vs. basal (two-way ANOVA on transformed data).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Basal</th>
<th>EHC</th>
<th>Lean Basal</th>
<th>EHC</th>
<th>Obese Basal</th>
<th>EHC</th>
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<tr>
<td>Adiponectin</td>
<td>0.98 ± 0.18</td>
<td>1.33 ± 0.15</td>
<td>0.93 ± 0.04</td>
<td>1.46 ± 0.49</td>
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<tr>
<td>AdipoR1</td>
<td>0.55 ± 0.16</td>
<td>0.38 ± 0.12</td>
<td>1.18 ± 0.43</td>
<td>1.41 ± 0.37</td>
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<tr>
<td>AdipoR2</td>
<td>0.59 ± 0.14</td>
<td>0.90 ± 0.09*</td>
<td>0.66 ± 0.05</td>
<td>0.72 ± 0.08</td>
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<tr>
<td>ERp44</td>
<td>2.61 ± 0.52</td>
<td>2.97 ± 0.34</td>
<td>2.29 ± 0.22</td>
<td>2.69 ± 0.30</td>
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<tr>
<td>Ero1-α</td>
<td>2.25 ± 0.42</td>
<td>2.39 ± 0.22*</td>
<td>2.48 ± 0.17</td>
<td>2.51 ± 0.24</td>
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<tr>
<td>GLUT4</td>
<td>0.55 ± 0.09c</td>
<td>0.97 ± 0.10d</td>
<td>0.34 ± 0.03</td>
<td>0.42 ± 0.08e</td>
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Data are mean ± SEM. The relative abundance of mRNA levels for each gene was normalized to 18s rRNA.

* P values: * P < 0.05 vs. lean EHC; † P = 0.07 vs. lean basal; ‡ P < 0.05 vs. obese basal; § P < 0.05 vs. lean basal; †† P < 0.001 vs. lean EHC.
more prominent in AT interstitial fluid (\(40\% \text{ vs. } 15\%\)) than in serum (\(40\% \text{ vs. } 15\%\)). This may imply that the regulatory mechanism underlying insulin-mediated hypoadiponectinemia is reflected in AT interstitial fluid. As opposed to the fasting state, the pattern of individual adiponectin isoforms \textit{in situ} and in the circulation differed in the obese group, implicating a differential response to insulin and/or IR of the cellular processing of adiponectin oligomers. Indeed, obese subjects failed to exhibit significant changes of HMW and trimeric circulating adiponectin, and the lowering effect of insulin was not accompanied by significant adiponectin gene changes or by variations of the two cellular chaperones. Altogether, these findings indicate that acute hyperinsulinemia may thus contribute to the obesity-linked decline of circulating HMW by reducing the production of basic adiponectin building blocks in adipocytes and, ultimately, impairing the cellular formation of the higher-order complexes.

Alternatively, the slower delivery rate of the interstitial HMW forms into the circulation (11) renders it possible for insulin to control the compartmental distribution of adiponectin complexes by selectively impeding the spill-over of the multimers. On the other hand, circulating HMW forms possess a longer half-life and lower turnover than the lower-order oligomers (6, 15, 16, 31). Thus, in the acute setting, insulin challenge might have increased the retention \textit{in situ} of the lower-order complexes, possibly explaining the decrease of the hexamers seen in obese subjects.

Another interesting finding in our study was the different response to hyperinsulinemia of GLUT4 and adiponectin receptors gene expression. Previous works from our laboratory emphasized the early association between AT dysregulation and IR (41, 42). Here, the inverse correlation between cell size, GLUT4, and glucose disposal extends the previous results and further underscores the role of enhanced terminal adipocyte differentiation in the modulation of systemic insulin sensitivity. Finally, the response of the AdipoR2 gene to insulin challenge suggests that this receptor may play a role in mediating the effect of adiponectin in AT in relation to insulin sensitization (43).

There are also study limitations that need to be discussed. First, the interstitial adiponectin levels did not mirror the actual tissue concentrations because the values were not adjusted for the recovery factor, explaining the apparently lower adiponectin levels in interstitial fluid than in serum (27). However, by evaluating inulin kinetics (24, 44, 45), an external recovery marker, we showed stable \textit{in vivo} recoveries and unaltered membrane efficiency in each subject throughout the duration of the experiment (data not shown). Accordingly, relative recovery adjustment results in an equal multiplication of the dialysate level, and we found similar \textit{in vivo} recovery rates between lean and obese individuals (24). Nonetheless, the temporal resolution of the technique is of importance to detect a correct trend when changes from baseline levels are ad-
dressed (25). Second, although the characterization of interstitial adiponectin in the sc abdominal AT may not reflect the activity of the whole-body fat, different data indicate that this depot exerts a greater influence on circulating adiponectin than the visceral fat (2, 34, 35, 46). Third, the nonreducing SDS-PAGE may be technically challenging to quantify precisely the adiponectin oligomers also because the Alb-LMW is difficult to separate from the other forms (1, 9). However, the resolution power of SDS-PAGE was reported not to be inferior to that of gel filtration (30), and with our experimental conditions, a high technique-inherent variability of the results appears unlikely. Finally, due to the small sample size, we may have missed significant differences or associations between the groups.

In conclusion, the current work suggests that acute hyperinsulinemia may differentially affect the compartmental distribution of adiponectin complexes in lean and insulin-sensitive vs. obese and IR subjects. Further studies are, however, needed to unravel the sensitivity to insulin of the adipocyte cellular machinery as well as the molecular mechanisms of interstitial adiponectin transport.

Acknowledgments

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