Circulating and Adipose Levels of Adipokines Associated With Insulin Sensitivity in Nonobese Subjects With Type 2 Diabetes

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Context: The adipokines chemerin, dipeptidyl peptidase 4, and adiponectin influence insulin sensitivity. Whether their circulating levels and adipose secretion are altered in nonobese individuals with type 2 diabetes mellitus (T2DM) is unknown.

Objective: The objective of this study was to investigate SC adipose secretion and serum levels of the three adipokines in relation to T2DM features.

Design: Fourteen nonobese T2DM and 13 healthy men were investigated. Insulin sensitivity and glucose control were assessed by hyperinsulinemic euglycemic clamp, homeostasis model assessment, and glycated hemoglobin.

Main Outcome Measure: Association of circulating and adipose-secreted adipokines with fat cell volume and insulin sensitivity was measured.

Participants: Volunteers in an outpatient academic clinic participated.

Results: Although adipose secretion was similar between the groups, serum chemerin was higher (70 ± 11006 10 vs 50 ± 1006 1 ng/ml; \(P = .005\)), adiponectin lower (4.7 ± 1.3 vs 6.8 ± 2.2 \(\mu g/ml; P = .005\)), and dipeptidyl peptidase 4 unaltered in T2DM. Serum adiponectin (\(r = 0.53; P = .005\)) and chemerin (\(r = 0.42; P = .03\)) correlated with adipose secreted levels. Secreted and circulating chemerin correlated positively with adipocyte volume (\(r = 0.40; P < .05\)), whereas serum adiponectin correlated negatively with this measure (\(r = 0.61; P = .001\)). Adiponectin serum half-life was decreased in T2DM (168 ± 24 vs 186 ± 18 minutes; \(P = .029\)) and correlated negatively with glycated hemoglobin (\(r = 0.45; P = .03\)) and adipocyte volume (\(r = 0.56; P < .003\)). Serum adiponectin (\(r = 0.57; P = .017\)) and chemerin (\(r = 0.52; P = .03\)) associated with clamp measures independently of T2DM diagnosis.

Conclusions: In nonobese men, circulating adiponectin and chemerin levels are altered in T2DM without changes in adipose secretion. Adipocyte volume is important for variations in serum chemerin and adiponectin and for serum clearance of adiponectin. In T2DM, poor glucose control also plays a role for adiponectin clearance. (J Clin Endocrinol Metab 101: 3765–3771, 2016)

The strong association between excess white adipose tissue (WAT) and development of type 2 diabetes mellitus (T2DM) suggests that intrinsic factors in WAT (eg, increased fat cell size and/or tissue inflammation/fibrosis) could be of pathophysiological importance. In this respect, WAT secreted proteins (adipokines) that influence insulin sensitivity and glucose control may fuel ongoing insulin resistance and thus contribute to the development of T2DM. Current evidence for this notion includes a number of studies that have demonstrated alterations in serum adipokine levels in T2DM compared with healthy controls. However, whether these alterations in serum adipokine levels reflect changes in adipose tissue secretion remains unclear, and whether the levels of circulating adipokines are associated with indexes of insulin sensitivity and glycemic control in nonobese individuals with T2DM is unknown. Therefore, in this study, we investigated whether serum and adipose-secreted levels of chemerin, dipeptidyl peptidase 4, and adiponectin were altered in a group of nonobese men with T2DM compared with healthy men. We also assessed the association between these serum and adipose-secreted adipokines and indexes of insulin sensitivity and glucose control.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; DPP4, dipeptidyl peptidase 4; ESAT, estimated SC adipose tissue; EVAT, estimated visceral fat; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment for insulin resistance; T2DM, type 2 diabetes mellitus; WAT, white adipose tissue.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA.
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Received April 13, 2016. Accepted August 3, 2016.
First Published Online August 8, 2016.
ence insulin sensitivity and thereby T2DM development could be of clinical significance. Indeed, as reviewed (1, 2), numerous studies in murine models as well as in man have demonstrated that many adipokines are altered in T2DM. However, as T2DM is most often associated with obesity and the latter exerts a profound influence on WAT release and circulating levels of adipokines (3), it remains unclear whether these changes are causal or not. This issue is of considerable clinical importance to fully understand the role of WAT in T2DM development.

In the present study, we aimed to investigate if T2DM associates with different adipokines linked to insulin sensitivity in an obesity-independent manner. For this purpose, we reinvestigated a cohort of nonobese men with or without T2DM (4). Several adipokines are known to influence insulin sensitivity in mouse models. In this clinical study, the focus was on three adipokines, adiponectin, chemerin, and dipeptidyl peptidase 4 (DPP4), which all have been shown to affect insulin action in their respective target tissues in man (5–10). The adipose secretion in vitro and serum levels of adiponectin, chemerin, and DPP4 were determined and related to in vivo measures of insulin sensitivity/glucose control and fat cell volume. For adiponectin, we also determined its serum half-life (11).

Materials and Methods

Subjects. We reinvestigated abdominal SC (WAT) and fasting serum obtained from a recently described cohort of 14 nonobese men with T2DM and 13 healthy control men matched for age, body mass index (BMI) and body fat content as measured by bioimpedance (4). The study was approved by the regional Committee on Ethics at Karolinska Institutet in Stockholm, Sweden, and all men gave their oral and written consent to participate in the study. None of the patients with T2DM was treated with insulin or a glitazone. Insulin sensitivity was assessed by homeostasis model assessment (HOMA-IR) and hyperinsulinemic euglycemic clamp (M-value, which was measured in seven subjects with T2DM and 10 controls) and glucose control by glycated hemoglobin (HbA1c) as described (4). As expected, HbA1c and HOMA-IR were significantly higher and the M-values markedly lower in the subjects with T2DM (4). Some of the published clinical measures are also detailed in Table 1. Total body fat and android/gynoid (central/peripheral) fat ratio were measured by dual-energy X-ray absorptiometry (DEXA) using a GE Lunar iDXA with the software enCORE (version 14.10.022) provided by the manufacturer (GE Healthcare) (12). The software was also used to calculate estimated visceral fat (EVAT) in the android region from the following formula: total adipose fat mass in the android region = EVAT + estimated SC adipose tissue (ESAT) in the android region, as previously described (13). Determination of EVAT with this method shows a strong correlation \( r^2 \geq 0.95 \) with measures using computed tomography (13). Assessment of android fat mass by DEXA is widely used and well-accepted as a valid measure. As total android fat mass and EVAT are used to determine ESAT and both are valid measures, it follows that the calculation of ESAT should also be valid. ESAT was therefore calculated as total android fat minus EVAT. It should be noted that ESAT and EVAT values do not reflect the total size of the respective adipose regions but only a representative part of each depot.

Adipokine secretion. WAT protein secretion was measured exactly as described previously (4). In brief, explants of abdominal SC WAT were incubated in vitro for 2 hours and adipokine concentration in the incubation medium was determined (4). The values were expressed per tissue weight unit or per number of incubated fat cells (adipocytes) as described (4). Fat cell volume was measured exactly as described previously (4).

Adiponectin half-life. An estimate of adiponectin half-life was made using the methods developed for leptin (14) and adopted for adiponectin as described in detail elsewhere (11). In brief, the calculation was based on the following assumptions: 1) the lipid content of adipose tissue is 0.8 times the tissue weight; 2) abdominal SC WAT secretion rate of adiponectin is representative for all adipose depots in nonobese (although data from a study of Motoshima et al (15) show 30% differences in secretion rates between the visceral and the SC depots in obesity, it should be noted that in nonobese, who were presently studied, the visceral fat depot represents only a minor fraction of total body fat, whereas the SC region is by far the largest region); 3) in vitro secretion rates of adiponectin are about the same as in vivo se-

| Phenotype | Healthy | T2DM | P Value |
|-----------|---------|------|---------|
| Age, ya   | 57 ± 11.2 | 60.5 ± 9.1 | .37 |
| BMI, kg/m²a | 25.9 ± 1.4 | 26.6 ± 1.6 | .27 |
| Fasting plasma glucose, mmol/litera | 5.2 ± 0.5 | 7.1 ± 1.3 | <.0001 |
| HbA1c, mmol/molb | 35.8 ± 3.4 | 49.4 ± 8.7 | <.001 |
| Fat cell volume, picolitersa | 451.0 ± 109.5 | 586.6 ± 117.0 | <.01 |
| Percentage body fat | 25.2 ± 6.7 | 29.8 ± 6.2 | .12 |
| Android/gynoid fat ratio | 1.37 ± 0.33 | 1.45 ± 0.32 | .53 |
| Abdominal SC adipose tissue (ESAT), g | 0.79 ± 0.30 | 0.88 ± 0.25 | .39 |
| Visceral adipose tissue (EVAT), kg | 1.32 ± 0.72 | 1.78 ± 0.95 | .17 |

Values are mean ± SD and compared by unpaired t test.

a Obtained from a previous publication on this cohort (see Methods).
cretion rates; 4) adiponectin concentrations in plasma and serum are almost identical; 5) there is a positive correlation between circulating and secreted adiponectin; and, 6) plasma pool size in milliliters is 37 times body weight in kilograms (16). The plasma adiponectin pool size was calculated by multiplying plasma pool size with the serum adiponectin concentration. Fractional adiponectin clearance, $k$, was calculated by dividing whole-body adiponectin production rate by the plasma adiponectin pool size. Plasma adiponectin half-life is equal to $\ln 2/k$.

**Measurement of adipokine levels.** Commercial ELISA kits from Mercodia (adiponectin, catalog no. 10–1193–01) and RD Systems (DPP4, catalog no. DY1180, and chemerin, catalog no. DY1180) were used.

**Statistical analysis.** Values reported are mean ± SD. Values between groups were compared by unpaired $t$ test. Individual values were compared putting healthy and T2DM subjects together in single, multiple, or stepwise regression analysis. The interaction with T2DM diagnosis in these correlation analyses was tested with analysis of covariance (ANCOVA). Values for HOMA-IR were log transformed before analysis. This study was initially designed to compare fat cell volume between groups (4). We had 85% power to detect a 20% difference between groups for this measure at a $P$ value of <.05. In the present multivariate analysis, we had 80% power to detect a difference between the predictors (healthy/T2DM) at $P < .05$ with an effect size ($f^2$) of 0.41.

**Results**

Body fat distribution was measured by DEXA and results are presented in Table 1. There were no significant differences between groups in total body fat percentage, overall body fat distribution (ie, android/gynoid ratio [central/peripheral fat]), or EVAT and ESAT.

Values for WAT secretion and serum levels of adipokines in T2DM and controls are compared in Table 2. Serum adiponectin was significantly lower and serum chemerin significantly higher in T2DM. However, there was no between-group difference in WAT secretion of adiponectin or chemerin irrespective of whether secretion was related to tissue weight or number of incubated fat cells. For DPP4 there were no differences in either serum concentrations or WAT secreted levels between T2DM and control subjects (Table 2). All further examinations were therefore focused on serum adiponectin and chemerin. Based on secretion values for healthy subjects and current sample size, it was possible to detect an approximate 40% increase in chemerin secretion and approximate 30% decrease in adiponectin secretion in T2DM with approximately 80% statistical power using an $\alpha$-value of 0.05.

The relationship between WAT secretion and serum levels of adiponectin and chemerin, respectively, are depicted in

**Table 2. Serum Levels and Adipose Secretion of Adipokines in Nonobese Healthy or T2DM Subjects**

| Measure                              | Healthy    | T2DM       | $P$ Value |
|--------------------------------------|------------|------------|-----------|
| S-adiponectin, $\mu$g/ml             | 6.8 ± 2.2  | 4.7 ± 1.3  | .004      |
| S-chemerin, ng/ml                    | 57 ± 11    | 70 ± 10    | .005      |
| S-DPP4, ng/ml                        | 211 ± 133  | 286 ± 147  | .18       |
| Adiponectin secretion, ng/g lipid    | 188 ± 81   | 147 ± 47   | .12       |
| Adiponectin secretion, ng/10$^7$ fat cells | 713 ± 210 | 785 ± 279  | .47       |
| Chemerin secretion, ng/g lipid       | 18 ± 8     | 14 ± 5     | .10       |
| Chemerin secretion, ng/10$^7$ cells | 74 ± 37    | 76 ± 38    | .90       |
| DPP4 secretion, ng/g lipid           | 4.7 ± 1.5  | 4.6 ± 1.6  | .85       |
| DPP4 secretion, ng/10$^7$ cells      | 18.8 ± 6.6 | 24.5 ± 9.9 | .12       |

Abbreviation: S, fasting serum.

Values are mean ± SD and compared by unpaired $t$ test.

**Figure 1.** Relationship between adipose secretion and serum levels of adiponectin and chemerin. Values analyzed by linear regression analysis and ANCOVA.
There was no influence of T2DM diagnosis. Adipose secretion was strongly and positively related to serum adiponectin levels, which would be expected from the fact that adipose tissue is the principal source of adiponectin. In contrast, chemerin secretion and serum levels were negatively associated, suggesting that nonadipose sources are important contributors to the circulating levels.

As decreased serum adiponectin in T2DM could not be explained by decreased WAT production (Table 2), we assessed if other factors could be involved such as decreased plasma half-life. Indeed, the half-life was slightly but significantly lower in T2DM patients compared with control subjects (168 ± 24 and 186 ± 18 minutes, respectively; \( P = .029 \)). To investigate whether glucose control could affect adiponectin clearance, HbA\(_{1c}\) was related to the half-life values of adiponectin (Figure 2) in all subjects put together. A significant inverse relationship was observed, which was independent of T2DM diagnosis. As fat cell volume was increased in T2DM (Table 1), we examined the relationship between this measure and adipokine variables. Adiponectin half-life was negatively correlated with fat cell volume (\( r = -0.56; P = .003 \)) independent of T2DM diagnosis (Figure 2). Furthermore, there was a strong negative correlation between fat cell volume and serum adiponectin (\( r = -0.61; P = .001 \)), which was independent of T2DM diagnosis (\( F = 1.2 \)) (Figure 2). However, fat cell volume did not correlate with adiponectin secretion from WAT (\( r = 0.33, P = .10 \), graph not shown).

We also investigated the relationship between fat cell volume and chemerin (Figure 3). Fat cell volume correlated positively with chemerin secretion (\( r = 0.40; P = .036 \)) as well as with chemerin serum levels (\( r = 0.40; P = .036 \)). These relationships were not influenced by T2DM diagnosis (\( F = 0.40 \)).

The influence of BMI on the relationship between fat cell volume and adipokines was examined by multiple regression analysis. The relationships between half-life and circulating levels of adiponectin or between chemerin secretion and its serum levels remained significant after correction for BMI (partial \( r = 0.60, 0.79, \) and \( 0.50 \), respectively; \( P = .005, <.0001, \) and .028, respectively).

The relationship between serum adiponectin or chemerin and insulin sensitivity was investigated (Figure 4). For adiponectin, an inverse correlation with HOMA-IR and a positive correlation with the M-value were found. For serum chemerin, there was only a significant relationship (negative) with the M-value. All relationships were independent of T2DM diagnosis.

The relative influence of serum adiponectin and chemerin on M-values was examined by stepwise regression. Adi-
Adiponectin entered the equation as first step (F to remove = 7.1) and chemerin as second step (F to remove = 5.4).

### Discussion

In this study, we investigated whether adipokine levels associate with T2DM and insulin resistance independently of obesity. Our findings suggest that differences in serum adiponectin and chemerin in T2DM are not secondary to excess body fat mass. Circulating protein levels are determined by the balance between tissue release rate and clearance rate from the circulation. Surprisingly, we observed no differences in the corresponding in vitro WAT release rates of adiponectin or chemerin between subjects with T2DM and healthy controls. This can be compared with previous studies using similar assay protocols where obesity was found to affect circulating and WAT secreted levels of chemerin and adiponectin to a similar degree (2, 3, 5, 6, 10). Adipocytes are the only important source for adiponectin (6). Therefore, it is likely that clearance of this adipokine from circulation could at least in part explain the low serum levels in T2DM. We found that, on average, serum half-life was decreased by about 20 minutes in the subjects with T2DM. This change may seem small bearing in mind that normal half-life was about 190 minutes in this study and 150 minutes in our previous investigation of healthy nonobese T2DM patients. As reviewed, chemerin is produced in several tissues besides adipose tissue such as the liver (20). Nevertheless, both chemerin secretion and its circulatory levels were positively correlated with fat cell size. The former was independent of BMI. This indicates that the elevated fat cell size observed in our examined patients impacts on adipose chemerin release in nonobese individuals with T2DM.

As adipose secretion did not explain the differences in serum levels, it is likely that other mechanisms may influence the circulating concentrations of adiponectin and chemerin in nonobese T2DM subjects. The negative relationship between circulating and WAT secreted chemerin suggests that nonadipose sources are important for the elevated serum chemerin levels observed in nonobese T2DM patients. As reviewed, chemerin is produced in several tissues besides adipose tissue such as the liver (20). Nevertheless, both chemerin secretion and its circulatory levels were positively correlated with fat cell size. The former was independent of BMI. This indicates that the elevated fat cell size observed in our examined patients impacts on adipose chemerin release in nonobese individuals with T2DM.

Both adiponectin and chemerin seem important for insulin sensitivity in nonobese subjects with or without amount of visceral WAT is small in nonobese subjects. Second, for adiponectin, visceral fat has a smaller impact on the circulating levels because the secretion rate in this depot is lower than that of the SC region (15, 17). Third, although the release of chemerin (and DPP4) is elevated in visceral compared to SC WAT, the regional differences are small (18, 19). The fat distribution measurements with DEXA showed no significant difference between groups in any variables, although T2DM patients tended to have more visceral, abdominal SC and total fat mass. It is therefore possible that secretion of chemerin from all fat depots put together is higher in nonobese subjects with T2DM than in healthy subjects.

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Both adiponectin and chemerin seem important for insulin sensitivity in nonobese subjects with or without...
T2DM. However, a diabetes diagnosis per se appears not to play an important role as the levels of both adiponectin and chemerin associated with insulin sensitivity in a similar fashion in nonobese T2DM and healthy subjects. This conclusion is based on the ANCOVA analysis of interaction with T2DM diagnosis in the regression analysis. Admittedly, we had only statistical power to detect a strong interaction. To observe weaker interactions, we would have needed several hundred individuals. Unfortunately, the paucity of nonobese T2DM among Caucasians precludes such large investigations. The negative association between serum adiponectin and insulin sensitivity in the present cohort confirms previous results in nonobese Japanese patients with T2DM (21); however, there were no control subjects in that study. Interestingly, nonobese relatives to patients with T2DM have decreased levels of serum adiponectin (22). In the present study, a direct comparison of adiponectin and chemerin showed that only the former correlated with both the M-values and HOMA-IR and when examined together adiponectin displayed a stronger association with M-value than chemerin. These results suggest that in nonobese individuals adiponectin is more closely associated with insulin resistance than chemerin, a speculation which needs to be supported by mechanistic studies in humans.

As opposed to the two previously mentioned adipokines, there was no significant impact of T2DM on circulating or WAT secreted levels of DPP4. This suggests that excess fat mass is the most important factor explaining the link between DPP4 and diabetes/insulin resistance previously reported in obese subjects.

The values for adipose chemerin secretion shown herein are much higher than those previously reported by us using in vitro incubated SC WAT (19); approximately 10 vs approximately 70 ng chemerin/2 hours incubation/10^7 fat cells. A possible explanation is that we in the former study used the only commercially available ELISA method from BioVendor, which at that time was only optimized for analyses of serum samples.

There are some caveats with the present investigation. We only investigated men. Gender differences in circulating or adipose release of adiponectin and DPP4 have been suggested by previous studies (19, 23). Second, the proteins are known to circulate in different forms with possible differences in biological activity. Herein, we only examined the total levels of the adipokines. Furthermore, we only investigated three adipokines associated with insulin sensitivity in man. Retinol binding protein 4 is also suggested to have an important role in this respect, but the results in clinical studies have been contradictory (24).
addition, commercially available kits for measuring its circulating levels have been criticized for lack of assay specificity (25). We therefore excluded retinol binding protein 4 in the present investigation.

In summary, circulating levels of adiponectin and chemerin but not of DPP4 are altered in nonobese subjects with T2DM. This is not readily explained by differences in the secreted levels from SC WAT. However, increased fat cell volume seems important and, for adiponectin, decreased serum half-life, in particular among T2DM patients with poor glucose control and enlarged fat cells, could also play a role.

Acknowledgments

The authors thank research nurses Katarina Hertel and Yvonne Widlund as well as laboratory technician Kerstin Wahlén for excellent technical assistance.

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This work was supported by grants from the Swedish Research Council, Novo Nordic Foundation, CIMED, Swedish Diabetes Foundation, Lisa and Johan Gröninger Foundation, Swedish Endocrine Society, Stockholm County council, Karolinska Institutet, and the Diabetes Research Program at Karolinska Institutet.

Disclosure Summary: The authors have nothing to disclose.

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