


# Correlation of Adiponectin With Testosterone in Patients With and Without Type 2 Diabetes and Erectile Dysfunction

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## Abstract

The aim of this study was to evaluate the levels of adiponectin in diabetic patients with and without erectile dysfunction (ED). In addition, the correlations of adiponectin with the scores of international index of erectile function (IIEF) and total testosterone levels were explored in diabetic and nondiabetic patients with ED. The study included three groups: Type 2 Diabetic patients (T2DM) with and without ED and a third nondiabetics with ED group, each of 29 patients. Fasting blood glucose (FBG), fasting insulin (FI), homeostasis model assessments of insulin resistance (HOMA-IR index), testosterone and adiponectin levels were evaluated. IIEF was applied to diabetic and nondiabetic patients with ED. The results showed that adiponectin was lower in diabetic patients with ED than in both nondiabetics with ED and diabetics without ED groups ( $5.23 \pm 1.05$  vs.  $11.38 \pm 10.08$  and  $6.5 \pm 2.13$ ;  $p = .003$  and  $.006$  respectively). Testosterone was lower in diabetic patients with ED than in diabetics without ED group ( $2.52 \pm 1.15$  vs.  $4.1 \pm 1.46$ ;  $p = .024$ ). Testosterone had a direct correlation with adiponectin ( $r = .371$ ;  $p = .001$ ). Both adiponectin and testosterone levels did not correlate with IIEF. In conclusion, the decreased adiponectin and testosterone are associated with ED in T2DM. Testosterone has a direct correlation with circulating adiponectin while both have no correlation with IIEF.

## Keywords

adiponectin, diabetes, physiological and endocrine disorders, erectile dysfunction, sexuality

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Adiponectin is an adipocyte-derived cytokine that has an important role in the regulation of energy homeostasis, with antiatherogenic, anti-inflammatory and antidiabetic properties (Ghadge, Khaire, & Kuvalekar, 2018). Adiponectin levels are significantly lower in some insulin-resistant states such as obesity and type 2 diabetes mellitus (T2DM) and in patients with coronary artery disease (Nigro et al., 2014). Chronic renal failure, type 1 diabetes and anorexia nervosa are associated with increased plasma adiponectin (Diez & Iglesias, 2003, 2010).

T2DM is the most common form of diabetes, accounting for the majority (>85%) of total diabetes prevalence in the developing countries and the prevalence of T2DM in Egyptians less than 79 years of age is about 11.4% (Motawi, Salman, Shaker, & Abdelhamid, 2015). UK

data for 2004–2014 denote an increased incidence of T2DM in men and deprived populations (Zghebi et al., 2017). Further, data from the United States show that the overall incidence of diabetes is increasing by 4.8% annually among youth (Zimmet & Shaw, 2017).

Many studies have reported that men with T2DM had lower testosterone levels (Dhindsa et al., 2004; Kapoor,

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Aldred, Clark, Channer, & Jones, 2007) and testosterone replacement therapy improves insulin resistance and glycemic control in hypogonadal men (Dhindsa et al., 2016; Kapoor, Clarke, Channer, & Jones, 2007).

Erectile dysfunction (ED) is three times more prevalent and manifests earlier in diabetic patients compared to the normal population (Giugliano et al., 2010; Kiskac et al., 2015; Lu et al., 2009).

Adiponectin has a vasoprotective role through increasing the bioavailability of the potent vasodilator, nitric oxide. Decreased adiponectin in T2DM may contribute to altered cavernosal vasoreactivity and ED (Vaiopoulos, Marinou, Christodoulides, & Koutsilieris, 2012).

The relationship between adiponectin and testosterone in patients with T2DM is conflicting. While Rasul, Ilhan, Reiter, Baumgartner-Parzer, and Kautzky-Willer (2011) identified a positive correlation between serum adiponectin and testosterone, others have reported an inverse weak correlation (Bai et al., 2011).

Few studies have addressed the correlation between adiponectin and testosterone in diabetics with ED with inconclusive results (Derosa, Romano, Tinelli, D'Angelo, & Maffioli, 2015; Dozio et al., 2012).

The aim of this study was to evaluate the levels of adiponectin in diabetic patients with and without ED. In addition, the correlations of adiponectin levels with the scores of international index of erectile function (IIEF) and total testosterone were explored in diabetic and nondiabetic patients with ED.

## Patients and Methods

This cross sectional study was conducted from November 2013 to October 2015 on 87 Egyptian patients attending the outpatient clinics of Mansoura University Hospitals, Mansoura, Egypt. The participants were consecutively selected and were divided into three separate groups. Diabetic patients with (Diabetics ED) and without ED and a third nondiabetics ED group, each composed of 29 patients. All the participants are married and have a stable sexual marital relationship. The exclusion criteria were type 1 diabetes mellitus, history of anatomic abnormalities of the penis (Peyronie's disease), hypogonadism, pelvic surgery, previous history of clinical neoplasm or organ transplantation, active liver disease and hypo- or hyperthyroidism. None of the patients took medication that affects hormonal or immunological status within the last 3 months. A written informed consent was obtained from all participants. The study was approved by institutional review board of Mansoura faculty of medicine, Mansoura University (Registration number, R/15.12.83). The purpose and importance of the study were explained to each study participant. The study was carried out in compliance with the Helsinki Declaration in 1964 and its

later amendments. All patients undergone clinical assessment that included a medical history to identify the presence of factors associated with ED including age, T2DM duration, glycemic control, smoking, duration of ED as well as clinical examination.

Diabetic and nondiabetic ED patients were evaluated with the IIEF questionnaire. The IIEF is a validated, multidimensional, self-administered investigation that has been found useful in the clinical assessment of ED and treatment outcomes in clinical trials. A score of 0–5 is awarded to each of the 15 questions that examine the four domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction (Rosen, Cappelleri, & Gendrano, 2002).

Body mass index (BMI) was calculated using the following equation: weight (kg)/height (m<sup>2</sup>) (Daviglius et al., 2003). Waist circumference was measured by tape around abdomen using the uppermost border of iliac crest as the landmark of measurement.

## Laboratory Evaluation

Ten ml of venous blood was withdrawn with sterile disposable syringes and then transferred directly into labeled screw cap tube without anticoagulant. Blood sample tubes were allowed to clot for 30 minutes. The serum was separated aseptically from the clot using a sterile disposable transfer pipette, then it was transferred to a screw cap labeled vial and stored frozen at  $-20^{\circ}\text{C}$ .

Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), High density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) were determined. A modified Friedewald formula was used for calculating LDL by using 1/6 triglyceride to minus instead of 1/5 triglyceride in the standard Friedewald formula.

$\text{LDL} = \text{total cholesterol} - \text{HDL} - 1/6 \text{ triglyceride}$  (Puavilai & Laoragpongse, 2004).

Fasting insulin (FI) was measured in all samples by chemiluminescence on immunolite 1000 after 8 hr fasting. Insulin resistance (IR) was assessed by homeostasis model assessments of insulin resistance (HOMA-IR index) based on FBG and plasma insulin concentration for estimation of HOMA-IR as follows: Serum insulin ( $\mu\text{IU/ml}$ )  $\times$  fasting blood glucose (mg/dl)/405 (Matthews et al., 1985). Plasma testosterone was determined by the available commercial competitive assay kits on Modular Analytics E 170 (Roche Diagnostics, Indianapolis, United States).

Total serum adiponectin levels were determined by Human adiponectin enzyme-linked immunosorbent assay kit (ELISA) (Assaypro, Saint Charles, United States), according to the manufacturer's instructions. The sensitivity of the assay was 0.7 ng/ml.

**Table 1.** Comparison Between the Three Groups in Terms of the Demographic and Laboratory Data.

Variables	Diabetics ED (29) Mean ± SD	Diabetics without ED (29) Mean ± SD	Nondiabetics ED (29) Mean ± SD	p value
Age	51.7 ± 10.3	44.52 ± 10.79	48.5 ± 10.8	.031 <sup>§</sup>
BMI (kg/m <sup>2</sup> )	29.4 ± 6.7	23.87 ± 2.98	29.0 ± 3.2	.003* <sup>§</sup>
Waist circumference (cm)	96.9 ± 16.4	87.58 ± 22.53	71.62 ± 16.7	.02* <sup>§</sup>
Total-cholesterol (mg/dl)	194.3 ± 32.9	187.31 ± 49.52	189.7 ± 35.4	.53 <sup>§</sup>
LDL-C (mg/dl)	115.3 ± 19.5	95.20 ± 44.83	119.4 ± 25.9	.005* <sup>§</sup>
HDL-C (mg/dl)	54.1 ± 16.5	48.19 ± 4.65	48.2 ± 10.1	.07 <sup>§</sup>
TG (mg/dl)	129.5 ± 73.6	133.64 ± 59.12	127.3 ± 43.6	.311 <sup>§</sup>
Adiponectin (µg/ml)	5.23 ± 1.05	6.5 ± 2.13	11.38 ± 10.08	<.001* <sup>§</sup>
Testosterone (ng/ml)	2.52 ± 1.15	4.10 ± 1.46	3.2 ± 1.5	<.001* <sup>§¶</sup>
Duration of ED (month)	27.39 ± 6.64	–	25.21 ± 4.32	.15 <sup>#</sup>
IIEF	10.45 ± 4.27	–	10.93 ± 3.43	.328 <sup>#</sup>
FBG (mg/dl)	185.35 ± 63.59	157 ± 40.21	–	.04* <sup>#</sup>
Insulin (µU/ml)	7.88 ± 6.07	4.94 ± 4.25	–	.037* <sup>#</sup>
HOMA-IR	3.6 ± 0.39	1.92 ± 0.24	–	.001* <sup>#</sup>
B-cell function (%)	31.38 ± 22.85	24.59 ± 7.67	–	.834 <sup>#</sup>
Insulin sensitivity (%)	90.7 ± 36.36	149.11 ± 52.91	–	.001* <sup>#</sup>

Note. ED = erectile dysfunction; BMI = body mass index; LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol; TG = triglycerides; FBG = fasting blood glucose; HOMA-IR = homeostasis model assessments of insulin resistance.

\* $p < .05$  was considered statistically significant.

<sup>§</sup>Kruskal–Wallis test; <sup>#</sup>Mann–Whitney  $U$  test.

<sup>¶</sup>Using Mann–Whitney  $U$  test,  $p$  was .059 for testosterone of diabetics ED versus nondiabetics ED and .024 for testosterone of diabetics ED versus diabetics without ED.

## Statistical Analyses

Statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, version 22.0, Armonk, NY: IBM Corporation). Continuous variables were expressed as means ± standard deviation ( $SD$ ). Variables with a normal distribution were compared by  $t$ -tests. Nonhomogeneously distributed variables were compared by the Mann–Whitney  $U$  test. Categorical variables were compared using  $\chi^2$  test. Kruskal–Wallis test was used to compare the three groups (diabetics with and without ED and nondiabetics with ED) together. Correlations were performed using Pearson or Spearman correlation when applicable. Stepwise forward linear regression was used to detect the independent significant correlation between adiponectin and different variables to predict the contribution of each variable in its outcome.

## Results

Demographic and laboratory data of diabetics with and without ED and nondiabetics with ED groups are presented in Table 1.

Serum adiponectin levels were lower in diabetics ED than in nondiabetics ED ( $5.23 \pm 1.05$  µg/ml vs.  $11.38 \pm 10.08$  µg/ml,  $p < .001$  respectively). The difference of

testosterone was not statistically significant between diabetics and nondiabetics ED ( $p = .059$ ), while the difference was statistically significant when comparing diabetics with and without ED ( $p = .024$ ). The waist circumference was statistically significant lengthier in diabetics ED compared with nondiabetics ED. The diabetics ED had statistically significant higher BMI, waist circumference, LDL-C, FBG, FI and HOMA-IR than the diabetics without ED (Table 1).

Serum adiponectin and testosterone levels were lower in diabetics ED than in diabetics without ED. No significant differences had been observed between the diabetics ED and diabetics without ED groups regarding TC, HDL-C, and TG (Table 1).

HOMA-IR had positive correlations with age ( $r = .259$ ,  $p = .04$ ) and waist circumference ( $r = .476$ ,  $p = .001$ ). Testosterone showed negative correlation with BMI ( $r = -.314$ ,  $p = .001$ ). Adiponectin had positive correlations with HDL-C ( $r = .428$ ,  $p = .02$ ), and testosterone ( $r = .368$ ,  $p = .04$ ) (Table 2).

In diabetics ED group after controlling of age and BMI using stepwise forward linear regression, adiponectin still had a positive correlation with testosterone ( $r = .882$ ,  $p < .001$ ). The IIEF showed no significant correlation with either adiponectin or testosterone concentrations ( $r = .0129$ ,  $p = .248$ ;  $r = .264$ ,  $p = .086$  respectively) (Table 2).

**Table 2.** Correlations of Adiponectin, HOMA-IR, and Testosterone Levels With Different Variables.

Parameters	Adiponectin	HOMA-IR	Testosterone (ng/ml)
	( <i>r</i> ) <i>p</i>	( <i>r</i> ) <i>p</i>	( <i>r</i> ) <i>p</i>
<b>Age (years)</b>	-.063 .559	.259* .049	-.034 .693
<b>BMI (kg/m<sup>2</sup>)</b>	-.485* .008	.121 .365	-.314* .001
<b>Waist circumference (cm)</b>	-.552* .002	.476* .001	.092 .635
<b>Adiponectin (µg/ml)</b>	– –	-.054 .687	.371* .001
<b>FBG (mg/dl)</b>	-.393* .036	.357* .004	.155 .246
<b>Fasting insulin (µU/ml)</b>	-.501* .005	.955* <.001	.047 .270
<b>B cell function (%)</b>	-.201 .13	.264* .045	-.137 .305
<b>Insulin sensitivity (%)</b>	.143 .285	-.885* <.001	-.051 .704
<b>Testosterone (ng/ml)</b>	.368* .04	.127 .340	– –
<b>IIEF</b>	.129 .248	-.032 .814	.264 .086

Note. \* $p < .05$  was considered statistically significant;  $r$  = correlation coefficient.  
IIEF = international index of erectile function.

## Discussion

In this cross sectional study, the mean value of adiponectin in diabetics with ED patients was significantly less than that of both diabetics without ED and nondiabetics ED groups. These findings supported the previous report of decreased adiponectin levels in T2DM with ED (Derosa et al., 2015). Also, Dozio et al. (2012) evaluated adiponectin and leptin to adiponectin ratio and their correlation with hormonal and metabolic parameters in men with arteriogenic and non-arteriogenic ED. They reported reduced levels of adiponectin in both arteriogenic and non-arteriogenic ED compared with patients without ED. However, most of their patients were not diabetic. In contrast, Derosa et al. (2015) reported no significant difference of adiponectin levels between diabetic patients with and without ED. The variation of adiponectin levels in these studies could be attributed to ethnic variations (Mente et al., 2010), differences in the study populations and to the use of different techniques to detect the adiponectin with different sensitivities. Additionally, the polymorphism in adiponectin gene (Motawi et al., 2015), nutrition, exercise, or abdominal adiposity might also explain the variations in the levels of adiponectin concentration (Swarbrick & Havel, 2008; Ziemke & Mantzoros, 2010). It has been demonstrated that hypo adiponectinemia is associated with an increased risk of T2DM

development and an independent risk factor for endothelial dysfunction (Li et al., 2011; Lindsay et al., 2002). Specifically, adiponectin enhances endothelial nitric oxide synthase (eNOS) activity and increases NO production, which in turn improves endothelium-dependent vasodilation (Chen, Montagnani, Funahashi, Shimomura, & Quon, 2003). Furthermore, adiponectin also suppresses the production of proinflammatory chemokines, adhesion molecules and superoxide release induced by tumor necrosis factor (TNF) and oxidized LDL respectively (Kobashi et al., 2005; Motoshima, Wu, Mahadev, & Goldstein, 2004; Ouchi et al., 2000).

In addition, the high molecular weight form of adiponectin can protect endothelial cells from apoptosis by activation of adenosine monophosphate-activated protein kinase (AMPK) (Kobayashi et al., 2004).

Based on the previous findings, ED was significantly associated with obesity (76%) and controlling diabetes with weight loss has been reported to improve ED (Pauli et al., 2008; Tamler, 2009).

The negative correlations between adiponectin levels and BMI ( $p < .01$ ) observed in our study was in agreement with these previous findings and other studies (Kriketos, Gan, Poynten, Furler, & Chisholm, 2004; Pischon et al., 2004; Trujillo & Scherer, 2005).

Waist circumference is a better predictor of visceral fat than BMI and waist-to-hip ratio (Wei, Gaskill, Haffner, &

Stern, 1997). In the current study, the waist circumference was higher in diabetics ED patients compared with non-diabetics ED and diabetics without ED ( $p < .001$  and  $.02$  respectively). In addition, waist circumference had negative correlation with adiponectin ( $r = -.552, p = .002$ ). These findings supported that of Wannamethee et al. (2007) who identified a negative correlation between adiponectin and waist circumference and that of Yassin et al. (2015) who reported a strong association between waist circumference and the severity of ED in hypogonadal men. In addition, Wei et al. (1997) concluded that the waist circumference is the best predictor of T2DM compared to BMI and other anthropometric measurements.

In the current study, adiponectin showed significant negative correlations with LDL, TG, and FBG levels and a positive correlation with HDL levels. These results are in agreement with other studies evaluating the association between adiponectin and lipids in diabetics with cardiovascular disorders (Durrani, Shah, Khan, & Jan, 2015; Pischon et al., 2004; Schulze et al., 2005).

Current study reported that diabetics ED had lower testosterone and higher fasting insulin compared with diabetics without ED (Table 2). These results are in general agreement with other studies evaluating the glycometabolic profile among diabetics with ED (Derosa et al., 2015, 2012). In addition, Rabijewski et al. (2018) concluded that better health-related quality of life in middle-aged and elderly men with prediabetes is associated with higher testosterone. It appears that ageing, higher BMI and increased waist circumference in diabetics ED could contribute to the decreased serum testosterone levels in this group.

In diabetics ED after controlling of age and BMI, adiponectin still had a positive correlations with serum testosterone ( $r = .882, p < .001$ ). These findings are consonant with the findings of other studies identifying a positive correlation between adiponectin and testosterone (Akishita et al., 2010; Dozio et al., 2012; Rasul et al., 2011).

Generally, it appears that the interplay between testosterone, adiponectin, and glucose metabolism is complex, bidirectional, and may be linked with BMI in a way that makes the study of each metabolic contribution difficult (Høst et al., 2014). For example, the effects of testosterone treatment on adiponectin levels were conflicting, with one study has reported elevation (Heufelder, Saad, Bunck, & Gooren, 2009), others have showed reduction (Frederiksen et al., 2012; Kapoor, Clarke, Stanworth, Channer, & Jones, 2007; Lanfranco, Zitzmann, Simoni, & Nieschlag, 2004; Page, Herbst, et al., 2005). Moreover, some studies have noted no significant effect at all (Gianatti et al., 2014; Page, Amory, et al., 2005). Page, Amory, et al. (2005) explained the absence of an effect by the dual action of testosterone

that increases adiponectin levels while exerting a direct negative effect on adiponectin gene and protein expression. Therefore, it might be possible to speculate that the low levels of adiponectin are one more consequence, along with ED, of low testosterone levels in diabetics ED patients. However, this speculation needs further studies. Adding to the complexity of the effect of androgens on adiponectin, Yarrow et al. (2012) indicated that natural and synthetic androgens reduced circulating total adiponectin levels in a dose-dependent manner, while maintaining high molecular weight adiponectin in rodents. Even though animal experiments often do not necessarily translate into replications in humans, the interplay between testosterone and adiponectin still awaits further research. The lack of correlation between adiponectin and testosterone with IIEF in this study could be due to the low number of ED patients. A large sample size is advised to yield correlation that would be more conclusive.

It is noteworthy that components of HOMA-IR have been implicated in the pathophysiology of diabetic ED. For example, HOMA-IR was significantly higher in diabetics ED than in nondiabetics ED. This is consistent with the previous studies in men with arteriogenic ED versus non-arteriogenic ED (Dozio et al., 2012), men with organic versus non-organic ED (Aversa et al., 2008) and in men with self-reported ED (Weinberg, Eisenberg, Patel, Chertow, & Leppert, 2013). Additionally, in the current study, HOMA-IR correlated positively with age ( $r = .259, p = .04$ ) and waist circumference ( $r = .476, p = .001$ ) suggesting a potential role of the aging process known to be associated with increased total body fat mass (Dozio et al., 2012). However, Derosa et al. (2012) failed to find statistical significance between diabetics ED and diabetics without ED in terms of HOMA-IR.

This study has some limitations. The sample size is relatively small and no healthy control group was included. In addition, the cross-sectional nature of the study could not conclude a causal relationship between the association of low testosterone and adiponectin among diabetic ED patients. Future studies to assess the exact role of adiponectin in ED are warranted.

## Conclusions

In conclusion, the decreased adiponectin and testosterone are associated with ED in T2DM. Testosterone has a direct correlation with circulating adiponectin while both testosterone and adiponectin have no correlation with IIEF.

## Compliance With Ethical Standards

A written informed consent was obtained from each participant included in the study.

All procedures performed were in accordance with the ethical standards of the faculty of medicine, Mansoura University institutional review board (Registration number, R/15.12.83) and with the 1964 Helsinki declaration and its later amendments.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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