

**Erectile Dysfunction, Obesity, and Insulin Resistance and Their
Relationship with Testosterone Levels in Eugonadal Patients in an
Andrology Clinic Setting**

Pablo Knoblovits⁽¹⁾, Pablo R. Costanzo⁽¹⁾, Gastón J. Rey Valzacchi⁽²⁾, Mario G.
Gueglio⁽²⁾, Alberto O. Layus⁽²⁾, Andrea E. Kozak⁽¹⁾, Marta I. Balzaretta⁽¹⁾, León E. Litwak⁽¹⁾.

⁽¹⁾Endocrinology and ⁽²⁾Urology Departments. Hospital Italiano de Buenos Aires, Argentina.
Gascón 450, CABA, C1181ACH.

Running Title: Erectile dysfunction and insulin-resistance.

Correspondence:

Pablo Knoblovits MD
Endocrinology Division
Hospital Italiano de Buenos Aires
Gascón 450, C1181ACH
Tel (54-11) 49610610
Fax (54-11) 49621266
email: pablo.knoblovits@hospitalitaliano.org.ar

Abstract

Erectile dysfunction (ED) is associated with metabolic and endocrine diseases including obesity, metabolic syndrome (MS) and Type 2 Diabetes Mellitus (DM2). Insulin-resistance (IR), present in patients with obesity, MS and DM2, causes disturbances in the signaling pathways required for nitric oxide production with subsequent endothelial dysfunction. In addition, IR also appears to alter testosterone production. We evaluated in eugonadal ED patients: 1) the presence of obesity and IR; 2) testosterone levels and their association with obesity and IR and 3) the degree of ED according to the presence of IR. In a prospective study 78 eugonadal patients with ED (group P) were recruited and compared with 17 men without ED as a control group (group C). The erectile function was evaluated according to the International Index of Erectile Function 5 (IIEF-5). IR was measured by HOMA. IR was defined as a $HOMA \geq 3$. Results: patients with ED had a significant higher BMI, waist circumference (WC), HOMA values and prevalence of IR when compared to group C. Total (TT) and bioavailable testosterone (BT) levels were lower in group P compared to group C. There was a significantly negative correlation between HOMA and IIEF-5, HOMA and TT, WC and IIEF-5, WC and TT and between WC and BT. Group P patients with IR had a higher WC and lower IIEF-5 score when compared with patients in group P without IR. In conclusion: Patients with ED show a higher BMI, WC, and HOMA and lower levels of TT and BT. There is a negative correlation between erectile function and IR and abdominal obesity. The TT levels are lower in patients with increased BMI, WC and IR. However, a negative correlation was shown only between BT (biologically active fraction) and abdominal obesity.

Key words: *male sexual function, insulin, waist circumference, testosterone, obesity.*

Introduction:

Erectile dysfunction (ED) affects an important percentage of the masculine population, with a prevalence of 30 – 70 % between 40 and 70 years old males, with most of them due to organic causes (Feldman et al, 1994; Laumann et al, 1999). Amongst the factors associated with ED are depression, hormonal changes and vascular or neurological damage after trauma or surgery. ED is also associated with different endocrine-metabolic disorders like type 2 Diabetes Mellitus (DM2) and components from the Metabolic Syndrome (MS) like hypertension, obesity and dislipidemia (Costanzo et al 2008; Demir, 2006).

Erection is a neuromyovascular phenomenon, in which the nitric oxide (NO) released by nerve endings and endothelial cells, plays a key role. NO is produced from L-arginine through an enzymatic step in which the enzyme NO synthetase is involved. Once produced, NO stimulates guanylate cyclase

enzyme present in the smooth muscle. This enzyme induces the production of cyclic guanosine monophosphate (GMPC) from guanosine triphosphate (GTP). GMPC phosphorylation induces the release of cytoplasmic calcium, allowing smooth muscle relaxation from the corpus cavernous, with the consequent blood repletion (penis tumescence) (Barouch et al, 2002; Trussell and Legro, 2007).

Insulin-resistance (IR), present in most patients with obesity, MS and DM2, is a metabolic alteration that produces endothelial dysfunction determined by lower synthesis and release of NO, combined with a higher NO consumption in tissues exposed to high concentrations of reactive oxygen species (Cersosimo and De Fronzo, 2006). The reduction in NO levels affects the different arteries of the body impairing its vasodilator mechanism (Mc Farlane et al, 2001). It is conceivable that the endothelial dysfunction caused by IR is also present in the corpus cavernous of patients with ED, affecting the erectile mechanisms. A higher prevalence of insulin resistance in the ED population was observed in non control studies (Bansal et al, 2005).

A normal testosterone concentration is associated with an adequate insulin sensitivity (Holmäng et al, 1992; Marin, 1995; Boyanov et al, 2003). Many studies have demonstrated an association between hypogonadism and MS (Kupelian et al, 2006; Makhsida et al, 2005; Muller et al 2005) and between hypogonadism and IR (Kapoor et al, 2006; Pitteloud et al, 2005). In addition, lower testosterone levels predispose to ED (Buvat and Bou Jaoudé, 2006; Saad et al, 2007; Mikhail, 2006).

In this study, we aimed to evaluate: 1) the presence of obesity and IR; 2) the levels of testosterone and its relationship with obesity and IR and 3) the degree of ED according to the presence of IR, in an eugonadal group of patients with erectile dysfunction and in a group of men with normal erectile function (control group) in an andrology clinical setting.

Methods

Population:

We studied 78 males (group P) with ages ranging from 40 to 70 years, in a stable relationship during the last 6 months, who consulted for ED at the Andrology Division in our hospital. Patients were excluded if they had pharmacologic (onset of ED within 6 months of the beginning of treatment with any drugs described as associated with ED) or anatomic (Peyronie's disease) ED, hyperprolactinemia, hypogonadism (defined when BT < 0.8 ng/mL in two samples in different days), alcohol abuse, history of prostate or pelvic surgery, severe chronic illness and/or patients use of drugs that may interfere with laboratory results (eg: antiandrogens, corticosteroids, metformin and antilipemic drugs among others). Patients with previous diagnosis of type 1 or type 2 DM were

excluded because of the known association of these conditions with erectile dysfunction and of type 2 DM with insulin resistance and obesity.

As a control group we included 17 men with normal erectile function (group C) who consulted the same Division for benign prostate diseases. Groups were matched by ages.

Our intended sample according to our power calculation was 50 cases and 50 controls. Nevertheless, due to the high prevalence of IR, we achieved statistical significance with a smaller control group.

Anthropometric parameters:

- Weight (kg) and height (m) were measured in light weight clothing without shoes by standard procedures. Body mass index (BMI) was calculated according to the formula: weight (kg)/height (m²) and was considered normal when < 25 kg/m², overweight between 25 - 29,9 kg/m² and obesity when ≥ 30 kg/m².
- Waist circumference (WC) (cm) was measured with a measuring tape around the navel, in the standing position, with the subject breathing normally.

International Index of Erectile Function (IIEF-5):

Is a validated questionnaire to evaluate the ED degree, consisting of 5 questions with 5 possible answers each one, with a score from 1 to 5. Based on a possible total score of 25, a score < 21 indicates some degree of ED. The lower the score, the more severe the degree of ED; using the 21 cut-off value, the test has a 98 % sensitivity and 88 % specificity for diagnosing ED (Rosen et al, 1999).

Laboratory tests:

A venipuncture was performed between 08.00 and 10.00 h, and fasting blood samples were obtained. Platelet-free serum was obtained by centrifugation and immediately stored at -20 C.

- Total Testosterone (TT) was measured using an competitive RIA double antibody (RIA DSL), the lower limit of detection was 0.05 ng/mL, laboratory reference ranges: 2.8-8.8 ng/mL for adults males; the intra-assay coefficient variation was 7.5 % and inter-assay coefficient variation was 8.1 %.

- Bioavailable testosterone (BT) was calculated using TT and SHBG by the method of Vermeulen et al; reference ranges: 0.8-6.0 ng/mL.

- Prolactin was measured by chemiluminescence immunoassay on the Architect analyzer, the lower limit of detection was 0.6 ng/mL, the inter-assay coefficient variation was 4 %, reference range: 5-20 ng/mL.

- Insulin was measured using an in-house competitive RIA (Herbert and Bleicher modified) employing a polyclonal antiinsulin antibody from guinea pig, the tracer was porcine insulin with ^{125}I , the lower limit of detection was 2.5 uUI/mL, the intra-assay coefficient of variation was 5.1 % and inter-assay coefficient was 10.4 %.
- Glucose was measured by enzymatic-O₂ consumption.

A 2-h Oral tolerance glucose test (OGTT) using a 75 g glucose load was performed in all patients, regardless of their fasting basal glucose results, according to World Health Organization criteria. Serum glucose levels after a 120 minutes glucose (glu 120) load were considered normal when < 140 mg/dL, impaired glucose tolerance when ≥ 140 and < 200 mg/dL, and levels ≥ 200 mg/dL were consistent with DM2 (WHO, 1985).

Homeostasis Model Assessment (HOMA) index was calculated according to the formula: serum glucose (mg/dL) x insulin (uU/mL) / 405 (Matthews et al, 1985). IR was defined as a HOMA ≥ 3 . HOMA index provides a good correlation with the insulin sensitivity index assessed by the gold standard test, the euglycemic clamp.

Statistical analysis:

Data was analyzed using InStat Statistical Software (GraphPad, Software, version 3.01). Differences in the characteristics of patients with ED and control group were compared with a two-sample *t* test for continuous variables; categorical variables were compared using Chi square. Pearson's correlation coefficients were used to assess the relationship between serum concentrations of testosterone (TT and BT) and measures of adiposity (BMI and WC), insulin resistance (HOMA) and IIEF-5. Data are presented as the mean \pm SD. All P values quoted are two sided, and values below 0.05 were taken to indicate statistical significance.

Patients and subjects who participated as control group, signed an informed consent and the trial protocol was approved by the Ethics Committee of the Hospital Italiano.

Results:

From the 78 patients evaluated with ED (group P), two were excluded due to diagnosis of normogonadotrophic hypogonadism, and other two due to DM2 diagnosed by OGTT; no cases of hyperprolactinemia were detected. Mean duration of ED was of 3.8 ± 3.6 years. In group C, no cases of hypogonadism, hyperprolactinemia or DM2 were found.

Mean age was similar in both groups (60 ± 9.3 versus 55.8 ± 8.2 years, for groups P and C respectively; $p=0.09$). Patients of group P presented higher WC and greater BMI than men in group C.

In addition, a lower percentage of patients with normal BMI and a higher prevalence of obesity were found in group P (Table 1).

When comparing laboratory parameters, significantly higher insulin levels (21.9 ± 11.1 versus 16.8 ± 11.0 uU/ml; $p=0.04$) and HOMA (5.0 ± 2.9 versus 3.5 ± 2.5 ; $p=0.03$) were observed in group P. Insulin resistance was more prevalent in group P: 75.67 % compared to group C: 47.05 %, $p=0.04$. There were no differences in basal and 120 minutes serum glucose levels between group P and group C, respectively. TT and BT levels were lower in group P compared with group C (TT 4.2 ± 1.2 versus 5.5 ± 1.9 ng/mL; $p=0.02$ and BT 1.7 ± 0.6 versus 2.1 ± 1.6 ng/mL; $p=0.02$) (Table 2).

A positive correlation was observed between HOMA and BMI, $r: 0.32$, $p=0.002$, as well as between HOMA and WC, $r: 0.30$, $p=0.005$. A negative correlation was observed between HOMA and IIEF-5, $r: -0.21$, $p=0.004$ (Fig. 1); HOMA and TT, $r: -0.25$, $p=0.01$ (Fig. 2); BMI and TT, $r: -0.28$, $p=0.008$ (Fig. 3); BMI and IIEF-5, $r: -0.22$, $p=0.04$ (Fig. 4); WC and IIEF-5, $r: -0.23$, $p=0.03$ (Fig. 5); WC and TT, $r: -0.41$, $p<0.0001$ (Fig. 6) and between WC and BT, $r: -0.30$, $p=0.006$ (Fig. 7). There was no significant correlation between HOMA and BT, $r: -0.05$, $p=0.64$; BMI and BT, $r: -0.12$, $p=0.26$; TT and IIEF-5, $r: 0.17$, $p=0.11$ or between BT and IIEF-5, $r: 0.09$, $p=0.41$.

Patients in group P with IR (HOMA ≥ 3) presented higher WC (106.9 ± 10.3 versus 101.8 ± 10.7 cm; $p=0.04$), higher serum glucose levels (91.9 ± 12.3 versus 83.6 ± 14.8 mg/dL, $p=0.02$) and lower IIEF-5 score (13.7 ± 4.4 versus 16.2 ± 3.2 , $p=0.02$) compared with group P patients without IR (HOMA < 3). There were no significant differences in mean age, TT, BT and BMI between patients in group P with and without IR (Table 3).

Discussion:

Our findings demonstrate a higher degree of insulin-resistance in 40 to 70 years old men with erectile dysfunction, in comparison with men of the same age with normal erectile function.

In physiological conditions, insulin has an hemodynamic action: after crossing the endothelial barrier, insulin promotes the relaxation of the precapillary sphincter which induces vasodilation. As a result of this action, a greater number of microvessels are recruited, the capillary network expands and peripheral microvascular perfusion increases (Cersosimo and De Fronzo, 2006). The vasodilating action of insulin is exerted through NO synthesis in the endothelial cells, since insulin directly stimulates the expression and activation of NO synthetase.

Insulin-resistance is the physiopathological base of the metabolic and cardiovascular disturbances collectively known as metabolic syndrome. Hypertriglyceridemia and the increase of small and dense LDL cholesterol particles, contribute to the vascular damage and trigger an inflammatory response, resulting in monocyte's adhesion to the endothelial cells. The increased flow

of free glucose and fatty acids to the vascular smooth muscle cells and to the surrounding inflammatory cells stimulates an excessive formation of reactive oxygen and nitrogen species. Subsequently, the increase of free radicals in the mitochondria impairs NO production. In addition, insulin-resistance determines a lower synthesis and release of NO due to lower activity and expression of NO synthetase, which is combined with an accelerated consumption of NO during neutralization of oxidative stress (Cersosimo and De Fronzo, 2006; Mc Farlane et al, 2001).

Therefore, when insulin-resistance and disorders associated with glucose and lipids metabolism develop, a decrease in NO levels is observed, leading to an alteration in the vasodilation mechanisms mediated by the endothelium. This disruption in the normal endothelial vascular function, particularly in arterioles and capillaries, worsens the metabolic functions of insulin, producing a negative feedback mechanism.

It is likely that a similar endothelial dysfunction is also present in the cavernous bodies, impairing the erectile mechanisms (Jones et al, 2003; Jeremy et al, 2000; Sullivan et al, 1999). The small diameter (1-2 mm) and the relatively high content of smooth endothelial and muscular cells by unit of tissue volume compared with other organs, determines a higher cavernous arteries susceptibility to damage induced by oxidative stress (Kim et al, 2007).

Bansal et al evaluated the prevalence of insulin-resistance, measured by the Quantitative Insulin Sensitivity Check Index (QUICKI), in 154 men with erectile dysfunction. They reported a 79.2 % incidence of insulin-resistance in patients with erectile dysfunction, but without comparing them with a control group (Bansal et al, 2005).

We have also previously reported a greater prevalence of metabolic syndrome in patients with erectile dysfunction, when compared with a control group (Costanzo et al, 2008).

In this study, we observed a higher BMI and obesity prevalence in patients with erectile dysfunction in comparison with subjects with normal erection. The WC was significantly higher in patients with erectile dysfunction in comparison with the control group.

MS prevalence in patients with erectile dysfunction has been also evaluated in other studies, and a high prevalence of abdominal obesity has been found in these patients (Bansal et al, 2005; Corona et al, 2007; Bal et al 2007; Traish et al 2009). A prospective study carried out in Rancho Bernardo, after a 25 years follow-up, demonstrated that higher BMI was associated with a significant increase in erectile dysfunction risk (Fung et al, 2004).

As expected, a positive association between BMI and WC was observed with HOMA index. Our findings demonstrate a negative correlation between erectile function score and HOMA index, WC and BMI. Thus, the higher the degree of IR and obesity, the worse the erectile function would be. It has been reported that weight loss in obese patients with erectile dysfunction improves sexual

function, and it's associated with a lower concentration of endothelial dysfunction markers (Esposito et al, 2004). Kim et al demonstrated that the use of metformin therapy recovers the expression of enzyme NO synthetase in the penis of obese rats (Kim et al, 2007). Currently, there is no evidence available regarding the action of insulin-sensitizing agents on erectile dysfunction in men. Thus, insulin-resistance secondary to visceral obesity could result in erectile dysfunction through endothelial mediated dysfunction of the cavernous corpus, impairing vasodilation due to a reduced availability of NO.

Despite excluding patients with hypogonadism, our results have shown lower TT and BT levels in the group of patients with ED, compared to the control group with normal erectile function. We also find a negative correlation between TT levels and HOMA index, BMI and WC, whereas BT was negatively correlated only with the WC. These findings suggest that the lower TT levels observed in this group of patients are likely associated with a greater prevalence of obesity. Vermeulen et al found that BMI is an independent factor determining testosterone levels. The same authors also described a negative correlation between free testosterone levels and the percentage of body fat, abdominal fat and insulin levels (Vermeulen et al, 1999). The findings of lower TT levels in patients with ED and a negative correlation between TT levels and BMI, WC and HOMA can be associated with an impaired hepatic synthesis of sex hormone binding globulin, as it is usually seen in the presence of hyperinsulinemia (secondary to insulin resistance) and obesity (Couillard et al, 2000; Tsai et al, 2004; Abate et al, 2002).

Nevertheless, the negative correlation of BT with the WC and the lower BT levels found in patients with erectile dysfunction in relation to the control group, seems to confirm the importance of visceral obesity in total and bioavailable testosterone levels and suggests an endocrine action of the visceral fat tissue over the regulation of gonadal function.

Testosterone influences sexual activity by different mechanisms, which include the production of NO through ON synthetase stimulation. Since the patients evaluated in our study were eugonadal, it is unlikely that lower levels of testosterone, within limits of normal range, would favor a worse erectile function.

One limitation of our study is that results may not be applicable to the general population as patients and controls were recruited from an andrology clinic.

In conclusion, the present study shows a greater prevalence of obesity and higher degree of insulin resistance in patients with erectile dysfunction. A worse erectile function (lower score on IIEF-5) in patients with insulin-resistance and a negative correlation between erectile function score and HOMA index were also observed. These findings suggest a potential role of the metabolic disorder in the physiopathology of erectile dysfunction, as a result of endothelial dysfunction associated with the

impaired insulin action. Therefore, erectile dysfunction might be considered as a marker of vascular and metabolic damage, which could potentially evolve to overt cardiovascular disease and type 2 DM.

Acknowledgments

We are grateful to Professor. Claudio Benadiva, MD, from the Center for Advanced Reproductive Services, University of Connecticut Health Center, for his valuable suggestions and comments on this work.

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Tables

Table 1: Comparison of age, BMI and WC between both groups.

Table 2: Comparison of laboratory values and HOMA index between both groups.

Table 3: Comparison of anthropometric data, laboratory values, HOMA and IIEF-5 among patients with ED, with and without IR.

Figure legends

Fig. 1: Correlation between HOMA and IIEF-5 (r: -0.21, p= 0.004)

Fig. 2: Correlation between HOMA and TT (r: -0.25, p= 0.01)

Fig. 3: Correlation between BMI and TT (r: -0.28, p= 0.008)

Fig. 4: Correlation between BMI and IIEF-5 (r: -0.22, p= 0.04)

Fig. 5: Correlation between WC and IIEF-5 (r: -0.23, p= 0.03)

Fig. 6: Correlation between WC and TT (r: -0.41, p<0.0001)

Fig. 7: Correlation between WC and BT (r: -0.30, p= 0.006)

Table 1: Comparison of age, BMI and WC between both groups.

	Group P (n=74)	Group C (n=17)	p value
Age (years)	60.0 ± 9.3	55.8 ± 8.2	0.09
BMI (kg/m ²)	29.7 ± 4.4	26.2 ± 2.9	0.0004
BMI < 25 kg/m ² (%)	8.2	29.4	0.02
BMI 25-29.9 kg/m ² (%)	49.3	58.8	0.84
BMI > 30 kg/m ² (%)	42.5	11.8	0.04
WC (cm)	105.5 ± 10.6	98.1 ± 7.5	0.009

Values are presented as the mean ± SD.

Table 2: Comparison of laboratory values and HOMA index between both groups.

	Group P (n=74)	Group C (n=17)	p value
Glucose (mg/dL)	90.0 ± 13.3	85.9 ± 10.5	0.23
Glu 120 (mg/dL)	101.7 ± 35.8	88.0 ± 28.5	0.15
Insulin (uU/mL)	21.9 ± 11.1	16.8 ± 11.0	0.04
HOMA	5.0 ± 2.9	3.5 ± 2.5	0.03
IR (HOMA ≥ 3) (%)	75.67	47.05	0.04
TT (ng/mL)	4.2 ± 1.2	5.5 ± 1.9	0.02
BT (ng/mL)	1.7 ± 0.6	2.1 ± 1.6	0.02

Values are presented as the mean ± SD.

Table 3: Comparison of anthropometric data, laboratory values, HOMA and IIEF-5 among patients with ED, with and without IR.

	HOMA \geq 3 (n=57)	HOMA < 3 (n=17)	p value
Age (years)	62.5 \pm 9.7	59.3 \pm 9.1	0.20
Glucose (mg/dL)	91.9 \pm 12.3	83.6 \pm 14.8	0.02
Insulin (uU/mL)	25.4 \pm 10.3	10.8 \pm 3.7	<0.0001
HOMA	5.8 \pm 2.8	2.2 \pm 0.6	<0.0001
IIEF-5	13.7 \pm 4.4	16.2 \pm 3.2	0.02
TT (ng/mL)	4.1 \pm 1.2	4.5 \pm 1.1	0.22
BT (ng/mL)	1.7 \pm 0.7	1.7 \pm 0.6	0.94
BMI (kg/m ²)	30.0 \pm 4.5	28.6 \pm 4.0	0.13
WC (cm)	106.9 \pm 10.3	101.8 \pm 10.7	0.04

Values are presented as the mean \pm SD.

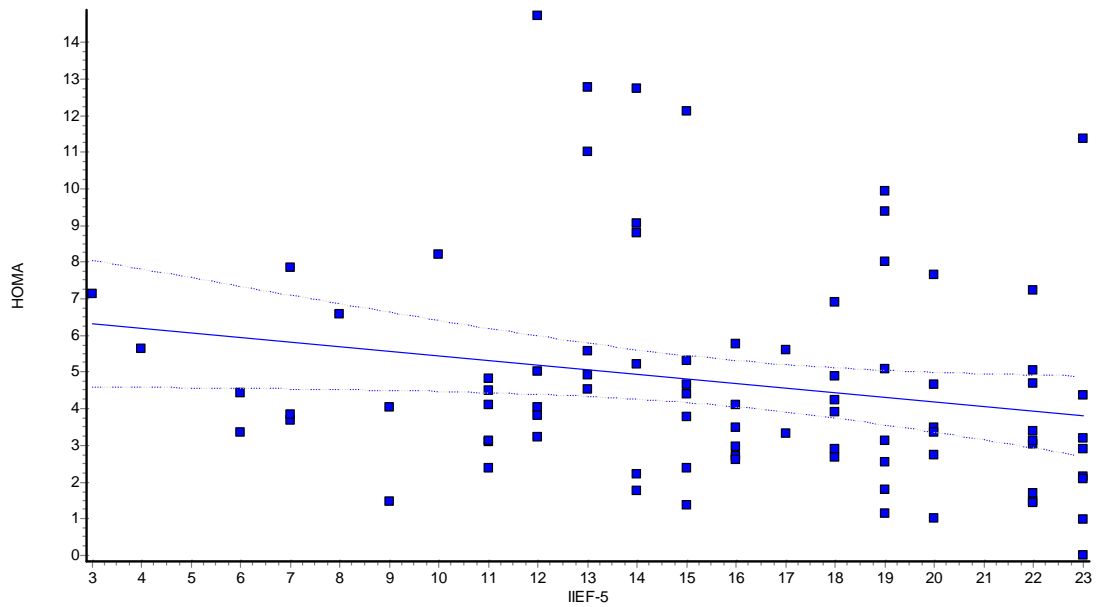


Fig. 1: Correlation between HOMA and IIEF-5 ($r: -0.21, p= 0.004$)

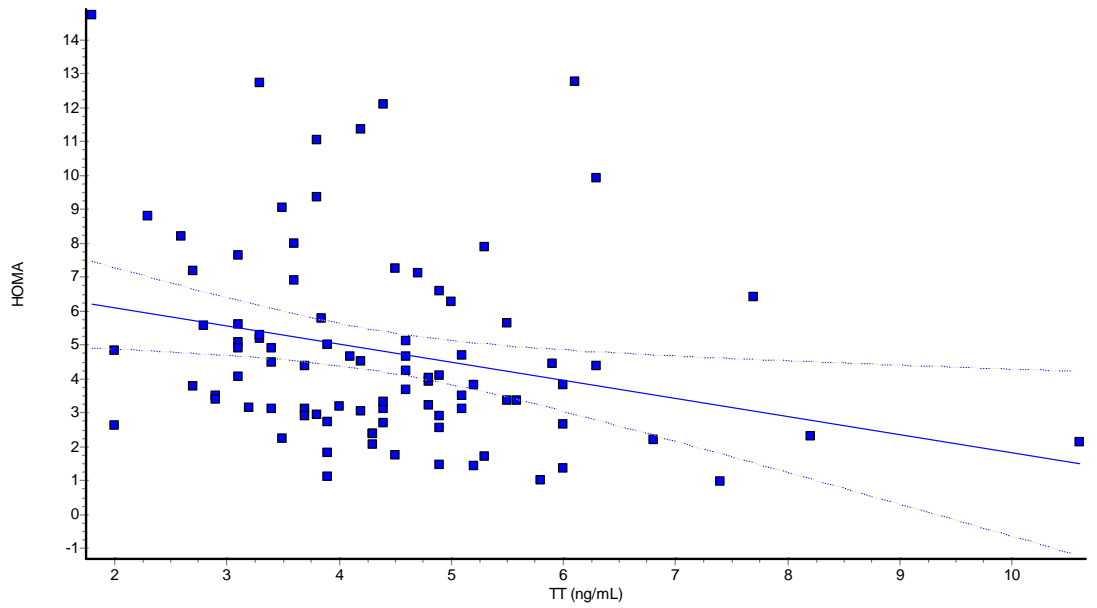


Fig. 2: Correlation between HOMA and TT ($r: -0.25, p= 0.01$)

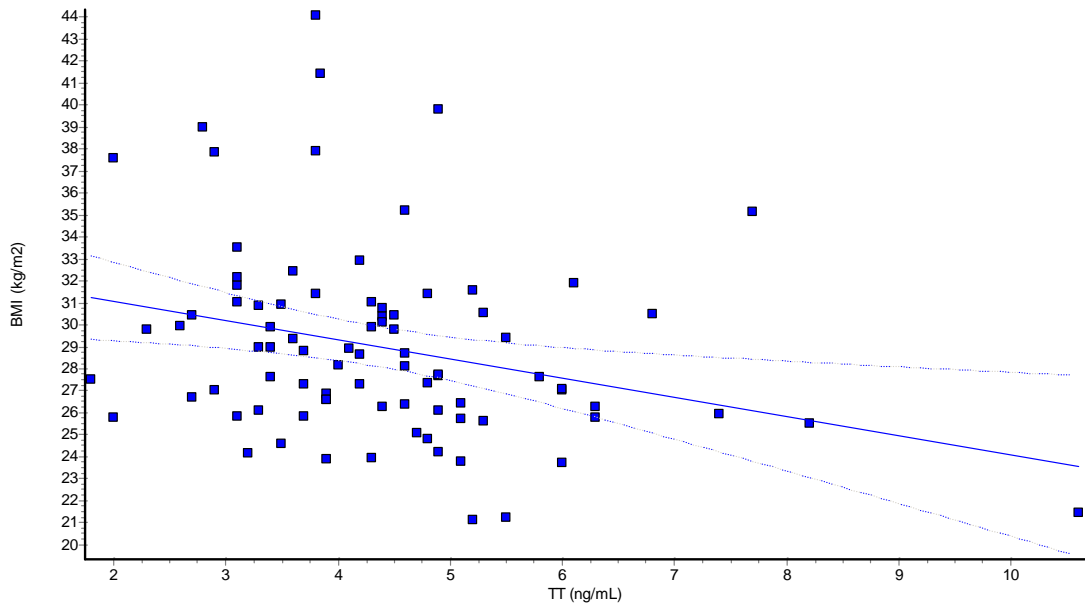


Fig. 3: Correlation between BMI and TT ($r: -0.28, p= 0.008$)

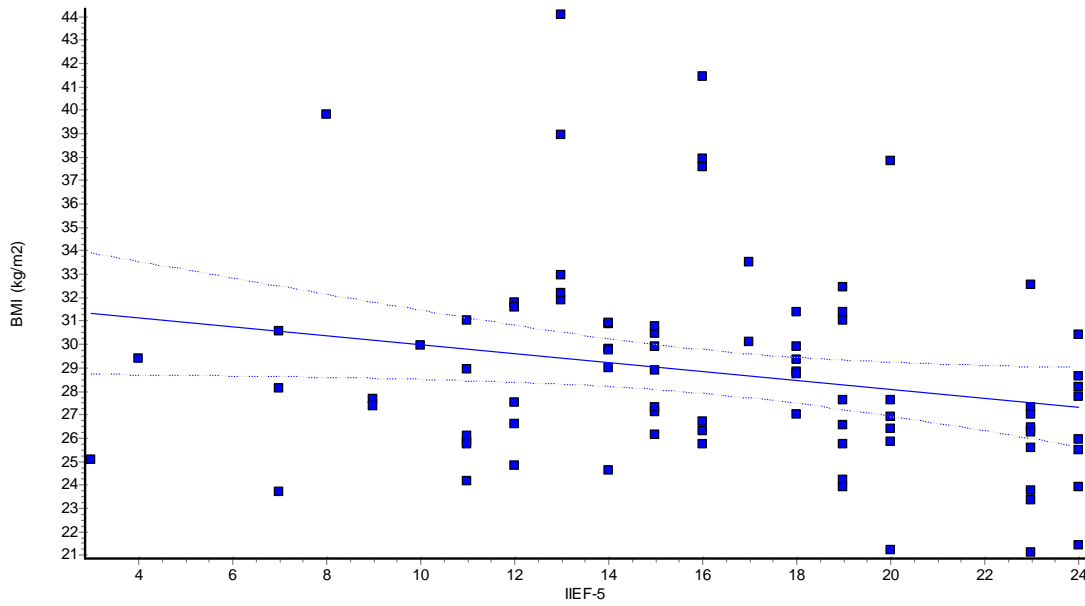


Fig. 4: Correlation between BMI and IIEF-5 ($r: -0.22, p= 0.04$)

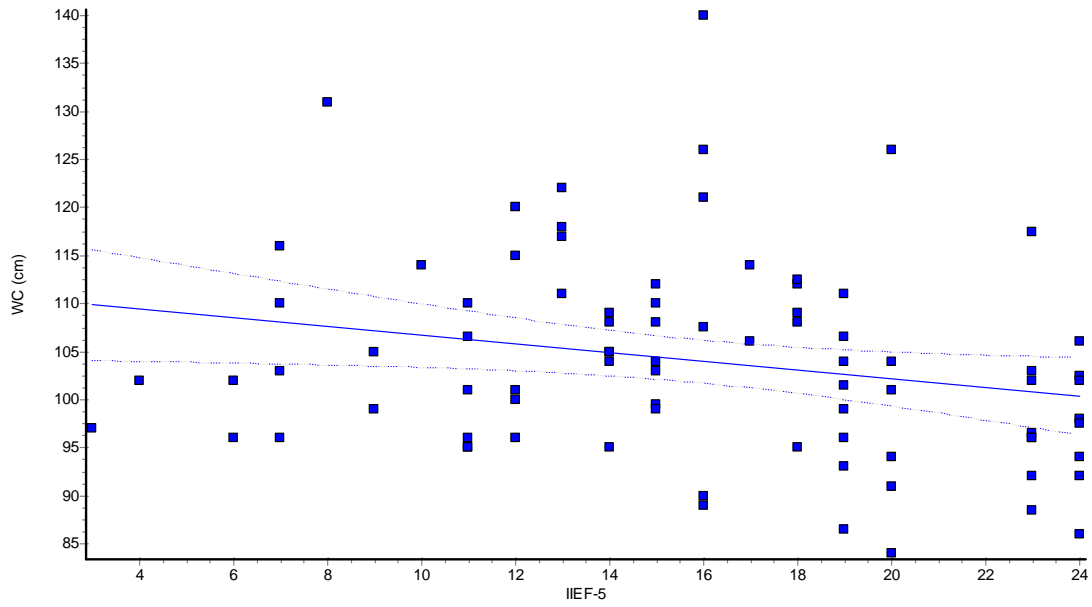


Fig. 5: Correlation between WC and IIEF-5 ($r: -0.23, p= 0.03$)

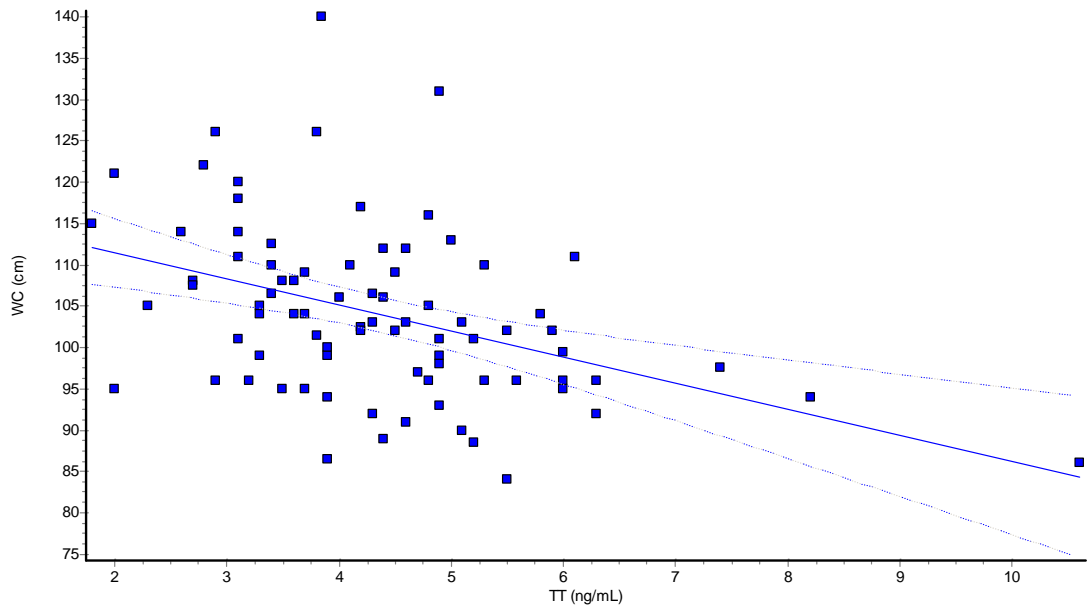


Fig. 6: Correlation between WC and TT ($r: -0.41, p<0.0001$)

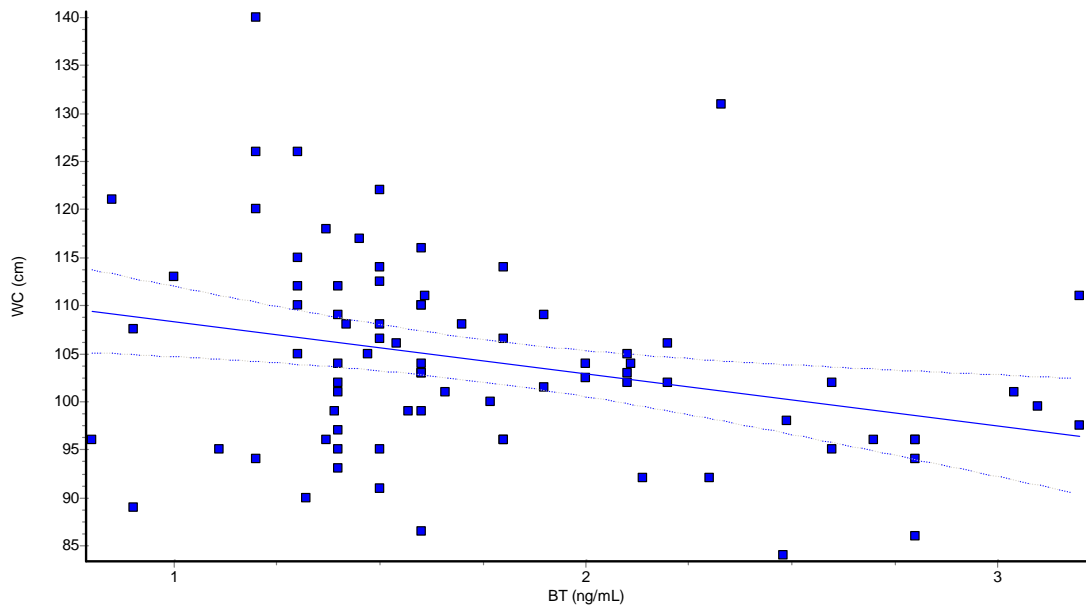


Fig. 7: Correlation between WC and BT ($r: -0.30, p= 0.006$)