Sexual dysfunction and central obesity in patients with first episode psychosis

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Abstract

Background
In recent years the association between sexual dysfunction (SD) and obesity in the general population has drawn major attention. Although sexual dysfunction is common in psychosis, its relationship with weight gain and obesity remains unclear.

Aims
To investigate the association between sexual dysfunction and obesity in a cohort of patients with first episode psychosis.

Method
Sexual function was assessed in a cohort of patients with first episode psychosis using the Sexual Function Questionnaire (SFQ). Anthropometric measures, including weight, BMI, waist, waist-hip ratio were investigated. Additionally, leptin and testosterone were investigated in male patients.

Results
A total of 116 patients (61 males and 55 females) were included. Of these 59% of males and 67.3% of females showed sexual dysfunction (SD) according to the SFQ. In males, higher SFQ scores were significantly correlated with higher BMI (Std. $\beta$=.36, $p=.01$), higher leptin levels (Std. $\beta$=.34, $p=.02$), higher waist-hip ratio (Std. $\beta$=.32, $p=.04$) and lower testosterone levels (Std. $\beta$=-.44, $p=.002$). In contrast, in females, SFQ scores were not associated with any of these factors.

Conclusions
While sexual dysfunction is present in both female and male patients with their first episode of psychosis, only in males is sexual dysfunction associated with increased BMI and waist-hip ratio. The association between SD, BMI, low levels of testosterone and high levels of
leptin suggest that policies that lead to healthier diets and more active lifestyles can be beneficial at least, to male patients.

Declaration of Interest

R.M.M. has received payment for speaking at symposia by BMS, Janssen and AZ. J.E. is an international medical manager at and employee of H. Lundbeck. F.G. has received honoraria for advisory work and lectures or CME activity support from Roche, BMS, Lundbeck, Otsaka, Janssen and Sunovion, is a collaborator on a NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including shares. F. has received honoraria for lectures from Janssen, Lilly and Bristol-Mayer Squibb. The other authors have no financial relationships with any organizations that might have an interest in the study in the previous 3 years.

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1. Introduction

The association between sexual dysfunction (SD) and heavier weight and obesity in the general population has recently drawn considerable attention\textsuperscript{1-3}. More specifically, erectile dysfunction in healthy males has been observed in association with obesity and other abnormal metabolic parameters\textsuperscript{1}, as well as with high levels of leptin and low levels of testosterone\textsuperscript{2,4}.

It is of interest that some of these factors, such as abnormal testosterone \textsuperscript{5} and increased leptin levels\textsuperscript{6} have also been reported as altered in patients with first episode psychosis, who also exhibit high rates of SD\textsuperscript{7}. For example, prevalence rates of up to 37 - 65\% of SD have been reported in patients with FEP \textsuperscript{7,8}. Furthermore, patients with FEP often present weight gain and metabolic abnormalities, mainly attributed to the use of antipsychotics\textsuperscript{9-12}.

A relationship between being overweight and central obesity on one side, and higher levels of leptin \textsuperscript{13} and lower levels of testosterone on the other has been proposed to explain the presence of hypogonadism and sexual dysfunction in the general population. According to this, the excessive circulating levels of leptin seen in the overweight might disrupt the steroidogenic function of the Leydig cells, with a subsequent reduction in hCG-driven testosterone production and testosterone deficiency as a final result\textsuperscript{4,14,15}. This testosterone deficiency has then been found to be associated with both hypogonadism and SD. \textsuperscript{2,3,16-18}

However, so far, few studies have investigated the potential causes of SD in FEP patients \textsuperscript{8,19}. To our knowledge, none has explored the relationship between SD, weight, testosterone, leptin and central obesity in patients with FEP. More specifically, no previous study has investigated whether hyperleptinaemia and testosterone deficiency may explain, at least in part, the sexual dysfunction often seen in patients with first episode psychosis; and how weight gain is associated with increased levels of leptin and decreased values of
testosterone and ultimately with sexual dysfunction. Studying these factors in patients at their first psychotic episode has several advantages: individuals have been exposed to medication for a relatively short period of time, and are less likely to suffer from residual and negative symptoms.

In a sample of patients at their first psychotic episode we investigated the following hypotheses: 1) that the presence of SD would be associated with being overweight, as indicated by higher weight and BMI, larger waist, waist-hip ratio; 2) that in male patients sexual dysfunction would be associated with overweight, lower testosterone and higher leptin plasma levels.

2. Methods

2.1 Design

This was a cross-sectional study of patients with first episode psychosis, conducted in the South London and Maudsley (SLAM) and Oxleas and Sussex Partnership NHS Trusts. The study was approved by the Ethics Committees of these Trusts (ref. # 1275/SUPA/2009).

2.2 Participants

Patients presenting for the first time to psychiatric services with a functional psychotic illness (ICD10: F=20-29 excluding coding F1x.0 for acute intoxication), psychotic symptoms lasting for at least 7 days and with an age between 18–65 years were approached from August 2008 to July 2011. Researchers screened for potential participants at the beginning of each week through a variety of means to ensure the maximum level of recruitment and minimise selection
bias. They took a list of all new admissions and screened clinical notes to assess for eligibility. Researchers attended weekly team meetings where the cases were discussed with doctors, nurses and healthcare assistants. Once a patient was deemed suitable, researchers would approach the potential participant and invited to participate in the study. The specifics of the project would be fully described and patients would be given the information and consent sheets. If patients were willing to participate and able to give informed consent, they were requested to read through the information sheet, invited to ask any questions and confirm that they fully understood the study and eventually sign the consent form.

Exclusion criteria were: presence of an organic psychosis, a moderate or severe learning disability (as defined by ICD-10 F=70-73, WHO, 1992), pregnancy, history of a medical or physiological cause of gonadal or sexual dysfunction (including hypothyroidism or other endocrine or metabolic disorder, vascular disorders and neurological disorders)\(^7, 22, 23\), lack of English fluency (requiring a translator), history of contact with health services (GP or mental health services) for psychosis beyond the previous 6 months.

A total of 286 patients consented to the study. Of the 286 potential patients at baseline, 27 were subsequently excluded for not satisfying the criteria for a first episode of psychosis or needing a translator, leaving a sample of 259 eligible participants. A further 40 patients dropped out leaving a final sample of 219 patients available for baseline assessments. At baseline, information on sexual dysfunction were available on 116 subjects.

### 2.3 Study Procedure
Sociodemographic data (age, gender, self-reported ethnicity, level of education attainment, and employment status) on subjects were collected using the Medical Research Council Social Scale. Medication histories were completed using information directly from patients and double checked with both inpatients and outpatients’ electronic records. Total days of exposure to antipsychotic medication was intended to be a lifetime exposure. This was calculated by converting the antipsychotic daily dose into chlorpromazine equivalent and multiplied for the total number of days the subject was exposed to antipsychotic- this was taken as a cumulative dose of antipsychotics. The date when the first prescription was issued was as start date and the date of completion of assessments and point of entry to our study was used as end date.

Antipsychotic doses were converted into chlorpromazine equivalents using established criteria. Daily and cumulative dose of antipsychotics was used as an indicator of impact of antipsychotics on sexual function and to determine whether there was a relationship between dose and outcome.

Sexual dysfunction was evaluated with the short Sexual Function Questionnaire (SFQ). The SFQ is a self-report structured instrument that has been previously validated in patients with psychotic disorders. Higher scores indicate greater impairment, and a total SFQ score equal or higher than 8 is considered a cut off indicating the presence of sexual dysfunction. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate psychotic and negative symptoms in patients with psychosis, as there is evidence of an association between sexual dysfunction and negative symptoms in patients with chronic psychosis. Depressive symptoms were assessed with Calgary Depression Score (CDS) as previous studies have shown that low mood can impact sexual function in the general population. Researchers with extensive training rated PANSS and CDS. Inter-rater
variability for PANSS and CDS was 0.95 and 0.96 respectively. A detailed history of illicit drug use (cannabis, stimulants, and any other recreational drug) was taken using the Cannabis Experience Questionnaire modified version\textsuperscript{31}. Anthropometric measures such as weight, waist, hip, waist-hip ratio, BMI were recorded on the day of assessment together with serum levels of prolactin, leptin and testosterone.

2.4. Laboratory Procedures

Patients were asked to fast and abstain from eating or drinking (except plain water) from midnight until 8 am of the day on which a blood sample was collected by an experienced phlebotomist. Samples were analyzed by the King’s Pathology Laboratory at King’s College Hospital, London.

Testosterone was analysed using a radio-immuno-enzymatic procedure that uses testosterone labelled with acridinium ester and an anti-testosterone antibody bound to paramagnetic particles to produce a light emission reaction. Intra-assay precision was calculated as Mean 3.31 (nmol/L) for Level 1 with CV of 6.2%. Sensitivity was 0.5 nmol/L. Reagents were provided by Siemens Healthcare Diagnostics Ltd.

Leptin was measured with a quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for leptin was pre-coated onto a microplate. Standards and samples were pipetted in duplicate for a minimum of 30 microL into the wells and any leptin present was bound by the immobilised antibody. After
washing away any unbound substances, an enzyme-linked monoclonal antibody specific for leptin was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells - colour develops in proportion to the amount of leptin bound in the initial step. The colour development was stopped and the intensity of the colour was measured. Intra-assay precision was calculated as mean 64.5 (pg/mL) with 2.14 SD and CV 3.3 %. The analytical sensitivity of leptin was 7.8 pg/mL. Elisa kit was supplied by R & D Systems Europe Ltd.

Prolactin was measured using Bayer Advia Centaur assay- which is a two-site sandwich immunoassay that uses direct chemiluminometric technology. Light intensity is measured and converted to light units. This has a direct proportional relationship with the prolactin concentration. Intra-assay precision was Mean: 69.9 (IU/L) with 2.6 % CV. Sensitivity was 6.4 IU/L. Reagents were supplied by Siemens Healthcare Diagnostics Ltd.

Anthropometric measures- namely weight, height, waist and hip circumference- were taken with subjects wearing light clothing and no shoes, and after having emptied their pockets. Waist circumference was measured by taking belly button as a point of reference, the tape measure was put on it and the patient was asked to wrap it around them. The measurement of the hip circumference was taken at the point yielding the maximum circumference over the buttocks, with the tap held in a horizontal plane touching the skin but not indenting the soft tissues.

2.5 Statistical analyses

In view of different female and male sexual physiology, analyses were conducted separately for each gender group. In both groups all variables were tested for normal distribution with
Kolmogorov-Smirnov test. The variables that did not follow a normal distribution were transformed using log-transformation or square root. In males those variables were: SFQ total score, prolactin and leptin serum levels and cumulative dose of antipsychotics. In females: prolactin serum levels, weight and hip and cumulative dose of antipsychotics. Exploratory partial correlations between SFQ and anthropometric and blood measures were conducted with daily and cumulative dose of antipsychotics, prolactin serum levels, PANSS, CDS as potential confounders. Only a p-value equal or less than 0.01 was accepted as significant to control for multiple testing.

Subsequently, regression analysis was used to calculate the association between SFQ and those outcome measures that reached statistical significance (less than 5%) in the exploratory analyses. Standardized beta (Std. β) is presented to allow comparison between variables and to assess the strength of the effect (Std. β of 0.14, 0.39 and 0.59 correspond to Cohen’s definition of small, medium and large effect sizes respectively) \(^{32}\). From the preliminary analysis only prolactin and PANSS total score were found to have an effect on outcome measures when used as covariates. CDS was therefore excluded from further analysis. Pearson correlation was also conducted between main outcome measures and covariates to identify those highly correlated and avoid problems of multicollinearity with the regression analysis. Waist-hip ratio, BMI, testosterone and leptin were also highly correlated; therefore, a separate linear multiple regression was performed for each, with SFQ as dependent variable and prolactin, cumulative dose of antipsychotics and PANSS total score as covariates.

3. Results

A total of 116 subjects (61 males and 55 females) were included in the analyses.
Demographic characteristics and values for each outcome variable are presented in Table 1. Of the patients included, 60 were Caucasians, 43 were Black African/African-Caribbean and 13 were of other ethnic background (7 of mixed ethnicity and 6 Asian). At the time of baseline assessments, a total of 102 subjects were taking antipsychotics (45 Olanzapine, 24 Risperidone, 21 Aripiprazole, 7 Quetiapine, 2 Haloperidol, 1 Amisulpride, 1 Sulpiride and 1 Trifluoperazine). Thirteen subjects were antipsychotic-naive and 1 patient had missing data. Among those prescribed with antipsychotics, the average duration of treatment with antipsychotics prior to assessment was 54 days (Std ± 55); the mean daily dose of antipsychotics, expressed as chlorpromazine equivalents, was 242.05 mg (Std. ± 178.01) while the mean cumulative dose of antipsychotic was 14690.03 mg (Std ± 17789.91). At the time of the baseline assessments, only 6 subjects were taking antidepressants (2 Sertraline, 3 Fluoxetine and 1 Escitalopram), 1 person was taking a mood stabilizer (sodium valproate) and 3 people benzodiazepines (clonazepam). Sixty-four subjects had been using cannabis before first contact with the services.

The subjects taking antidepressants were excluded from further analyses for small sample size as well as in view of the pronounced effects of selective serotonin re-uptake inhibitors on sexual function. 

The prevalence of obesity in male and female participants did not differ significantly (16.4 and 17.4 respectively, chi-square =0.019, df=1,p=0.891). Regarding obesity, we tested for mean differences in BMI with respect to medication. According to one way ANOVA there were no statistically significant differences (F(4.95)=0.104, p=0.981). With respect to sexual dysfunction, there were no statistically significant association to medication in males. For females, the association was significant (Fisher’s exact test: Chi=14.7273,
p=0.003). Specifically, among those who received olanzapine the percentage of those having sexual dysfunction was much higher than those who did not (48.6% versus 5.6%). This result however should be treated with caution as only 1 out of 19 women did not have sexual dysfunction (SFQ>=8). Additionally, among those who received aripiprazole, the percentage of those having sexual dysfunction was much lower than those who did not (10.8% versus 44.4%). No statistical differences were found for the rest of the antipsychotic medication.

The diagnosis was later ascertained using OPCRIT criteria with following results:
Schizophrenia 48.4%, Mania with psychosis 18.7%, Schizoaffective Disorder Depressive Type 5.5%, Schizoaffective Disorder Manic Type 4.4%, Depressive Episode Severe with psychotic features 8.8%, Moderate Depressive Episode 4.4%, Bipolar Affective Disorder 1%, Unspecified Non Organic Psychosis 1%, Delusional Disorder 1%, No criteria met 6.6%.

3.1. Correlation between sexual function and metabolic measures

A total of 59% males presented with SD, in comparison with 67.3% of women. Women showed higher dysfunction in reduction of sexual libido (N=30; 54.5%) and arousal (N=17; 30.9%), while men showed greater difficulty in achieving orgasm (N= 39; 63.9%).

3.1.1. Males
A partial correlation, with cumulative dose of antipsychotics, prolactin serum levels, and total score for PANSS as covariates showed that higher SFQ scores were significantly correlated with higher BMI (r=.39, p=.02) and increased leptin levels (r=.38, p=.02), and lower levels of testosterone (r=-.50, p≤ .003). Correlations with weight, hip and waist as other outcome measures were not significant (p-values > 0.05).

The measures, which reached statistical significance in this exploratory analysis, were entered in a linear multiple regression, with SFQ as dependent variable and PANSS, prolactin and cumulative dose of antipsychotics as covariates. Results showed that a larger waist-hip ratio (Std. β=. 32, p= .04; see Fig.1), higher BMI (Std. β=.36, p=.01; see Fig. 2) and increased serum leptin levels (Std. β=.34, p=.02) were significantly associated with higher scores of SFQ, with a marginal contribution to the model of prolactin serum levels (Std. β=. 29, p=.05). Lower levels of testosterone also significantly predicted higher SFQ scores (Sd. β=-.44, p=.002; see Fig. 3).

3.1.2 Females
In females, we performed a partial correlation between higher SFQ scores and anthropometric measures, including cumulative dose of antipsychotics, prolactin and PANSS scores together with CDS values as covariates. This showed no significant association between SD and any of the variable (all p-values > 0.05 with weight: r= .01 p=.46; waist: r=.10 p=.30; hip: r=.15 p=.23; waist-hip ratio: r= -.03 p=.43; BMI: r=.06 p=.37). Therefore, no regression analysis was performed.
4. Discussion

This is the first study to investigate the association between SD and ’an estimate of visceral fat’ in a cohort of patients with FEP. To our knowledge this is also the first study to report that waist-hip ratio and BMI are strong predictors of sexual dysfunction in male patients, and more importantly, to demonstrate an association between SD and testosterone and leptin levels in FEP. Our findings suggest that this effect is not simply mediated by antipsychotic exposure, since leptin and testosterone remained strong predictors of SD even when the exposure to antipsychotics was considered in the analysis. Our main finding is that SD is predicted by higher BMI and waist-hip ratio. While there are several reports\(^2-4,18\) indicating an association between visceral obesity and sexual dysfunction in the general population, there is none reporting such association in patients with psychosis

Being overweight has been correlated with hypogonadism in the general population\(^2\). In fact, hypogonadism may contribute to the accumulation of excess fat and to the reduction of insulin-sensitive muscular mass with increase in insulin resistance, leading to the onset of metabolic disorders\(^2\). It is proposed that men with SD, and/or with visceral obesity should be screened for testosterone deficiency and treated for weight reduction\(^35-37\). This would result in potential benefit in leptin reduction and increase of testosterone levels.

The second major finding of this study is that high levels of leptin and low levels of testosterone predict sexual dysfunction. This seems to be mediated by weight gain through leptin increase. Leptin is a cytokine released by adipocytes to regulate energy homeostasis\(^13\). It is possible that the weight gain -subsequent to antipsychotics load- is what induces leptin increase. In turn, leptin metabolizes testosterone to estradiol via an aromatase, with subsequent reduction of testosterone levels\(^4\). This facilitates the fatty acid uptake and triglyceride
storage. The overall result is an increase in fat stores, which further increases leptin production and subsequently increases aromatase activity. This drives the cycle even further, with higher levels of leptin and further reduction in testosterone concentration (for a review see 18). Isidori et al. 4 have clearly demonstrated that leptin concentrations are negatively correlated with total and free testosterone, and that leptin is a potent hormonal predictor of decreased androgen concentrations in obese men. They concluded that in obese men, high leptin concentrations inhibit the production of testosterone disrupting the steroidogenic function of Leydig cells. Therefore, low testosterone could be considered one of the many adverse consequences of being overweight and obesity².

Weight gain in patients with FEP seems to be associated with the use of antipsychotics 9-12. In order to prevent or reduce the risk of SD, use of weight inducing antipsychotics should be limited, when possible; alternatively, patients should engage in a variety of interventions like wellness programs, CBT, nutritional education and diet, weight management and exercise to improve physical health or health perception 38-44.

A recent meta-analysis by Bonfioli et al. 44 has demonstrated that when compared to treatment as usual, lifestyle interventions including diet and physical activity reduce weight in patients with psychosis by −0.98 BMI points. Unfortunately, despite the introduction of guidelines for metabolic screening in schizophrenia, metabolic monitoring in routine clinical practice is still unusual 46. Another interesting finding of this study relates to the female sample. Although a higher percentage of women presented with sexual dysfunction than males (67.3% vs. 59%), no association between SD and obesity or any other outcome measures was found. This may suggest that sexual dysfunction in women is not driven by fat excess or fat distribution. Males and females differ in terms of how and where body fat is stored, and also in the type of hormones they secrete in proportion to their fat 47.
Postmenopausal women seem to accumulate more fat in the intra-abdominal depot than do premenopausal women, and therefore are at greater risk of developing metabolic complications associated with obesity, similarly to men. Only 4 women in our study were postmenopausal and we did not study the testosterone and leptin cycle in this group since there is no evidence of such an association in the literature. Also, it is worth noting that the female sexual arousal response seems to be mediated, apart from testosterone, by several physiological modulators such as vasoactive intestinal polypeptide (VIP), nitric oxide (NO), and prostaglandin E (PGE) that regulate vaginal smooth muscle contractility. Future investigations of female sexual dysfunction should aim to investigate these factors.

Our results also indicate that prolactin marginally contributes to sexual dysfunction (Std. β=.29, p= .05). Although this finding is in line with some studies, is in contrast with others. Antipsychotics such as risperidone, amisulpride, and paliperidone induce higher prolactin levels and seem associated with higher incidence of SD compared to antipsychotics that do not (quetiapine, aripiprazole, ziprasidone, and olanzapine). However, some studies do not find differences in SD among patients taking different antipsychotics. In our sample, 39 males patients were taking prolactin-sparing antipsychotics and 15 were taking prolactin-elevating antipsychotics, while 6 were drug naive. Unfortunately, the number of patients taking prolactin-elevating antipsychotics was too small to allow a separate analysis to investigate the specific role of prolactin. These results should be therefore taken with caution.

Some limitations need to be considered when interpreting our findings. For example, we did not include a healthy control group. However, it is of note that similar clinical findings and molecular pathways have been proposed in non-psychotic male subjects in which SD has been associated with visceral obesity and mediated by leptin and testosterone.
Furthermore we believe is crucial to attract attention towards a more holistic approach to mental health which includes also sexual health. This subject is often disregarded amongst mental health professionals.\textsuperscript{54, 55} We think that offering new evidence of the pathophysiological mechanism that links fat tissues with testosterone metabolism\textsuperscript{3, 4} also in patients with mental illness at greater risks of sexual dysfunction due to increased risks of weight gain because of antipsychotic treatment needs to alert psychiatrists to put greater effort in reducing weight gain and promoting wellbeing and healthy living.\textsuperscript{39-46}

Also, we could not examine sub-domains of sexual function owing to power limitations, and so further studies are needed to determine whether there are particular domains of sexual dysfunction that are associated with metabolic abnormalities. Furthermore, we could not explore in details the impact of substance use on sexual dysfunction because of our sample size. However, an exploratory analysis on cannabis smokers did not show any impact of cannabis on male sexual function (data not shown). Nevertheless, the interaction between substance use and SD should be further investigated in larger samples.

In summary, impaired sexual function in male patients with first episode of psychosis is associated with visceral obesity, low testosterone and high leptin levels- independently of antipsychotic exposure. These preliminary results warrant an even more careful assessment of weight gain, fat distribution and sexual dysfunction in patients at the early stages of psychosis, since these conditions have a considerable impact on their quality of life and are probably a major factor in non-adherence to prescribed antipsychotic drugs\textsuperscript{53}. They also suggest that an earlier implementation of prevention strategies that provide healthier diets and more active lifestyles is required\textsuperscript{55, 56}. This type of intervention can help prevention of cardiovascular disease and promote higher fulfillment of such an important aspect of quality of life such as intimacy and sexuality.
Acknowledgements

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doi: 10.1016/j.schres.2016.05.017.
Table 1. Demographic characteristics of sample at baseline and main outcome measures

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<th></th>
<th>Total</th>
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<th>Females</th>
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<td>(n = 61)</td>
<td>(n = 55)</td>
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<td>Waist-hip ratio</td>
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<td>Waist (cm)</td>
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<td>Prolactin (mIU/L)</td>
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<td>Leptin (ng/mL)</td>
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<td>Testosterone (nmol/L)</td>
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Abbreviations: SD=Standard Deviation; Normal Values: Sexual Function Questionnaire ≤ 8; Calgary Depression Scale ≤ 5; Positive and Negative Syndrome Scale 30-210; Body Mass Index: 18-25; Waist-hip ratio: for Males ≥ .95; for Women ≤ .80; Waist: for Males ≤ 94 cm, for Women ≤ 80; Prolactin: 40-500 mIU/L; Leptin: for Males (2.21 – 11.15 ng/mL), for Females (3.88 – 77.27 ng/mL); Testosterone: for Males (10 - 30 nmol/L), for Females (0.5 - 2.6).
Fig. 1. Association between SFQ and waist-hip ratio in male patients with FEP. Linear trend line and 95% confidence interval of simple linear regression is plotted in the data.
Fig. 2. Association between SFQ and BMI in male patients with FEP. Linear trend line and 95% confidence interval of simple linear regression is plotted in the data.
Fig. 3. Association between SFQ and testosterone in male patients with FEP. Linear trend line and 95% confidence interval of simple linear regression is plotted in the data.