



Glucagon-like peptide-1 serum levels are associated with weight gain in patients treated with clozapine

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ABSTRACT

Metabolic syndrome and related cardiovascular risk factors are well-known comorbidities among patients with schizophrenia. Biomarkers of these antipsychotic-associated metabolic adverse effects and antipsychotic-induced weight gain are needed. Glucagon-like peptide-1 (GLP-1) is involved in insulin secretion, regulation of satiety, inhibition of food intake, and inhibition of gastric emptying. GLP-1 also induces reduction in body weight. Visfatin/ NAMPT/ PBEF is an adipocytokine secreted by several cells and tissues. Increased plasma visfatin levels have been associated with overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases, low grade inflammation, and proinflammatory markers. Associations between antipsychotic-induced weight gain and serum visfatin and GLP-1 levels have been little studied in patients with schizophrenia. The aim of the present study was to test the possible role of serum GLP-1 and visfatin level alterations as markers of weight gain in association with metabolic and inflammatory markers in 190 patients (109 male, 81 female) with schizophrenia on clozapine treatment. High serum levels of GLP-1 correlated significantly with higher levels of visfatin, leptin, insulin, HOMA-IR, higher BMI, and weight change among men. Associations between serum visfatin levels and BMI or weight change were not found in the present patients. Serum GLP-1 level seems to be a marker of metabolic risk factors among men with schizophrenia on clozapine treatment. Female patients may be more sensitive to suppressive effects of clozapine on GLP-1 secretion. Patients on clozapine would benefit from GLP-1 agonists as preventive treatment.

1. Introduction

Increased prevalence of metabolic syndrome and related cardiovascular risk factors are well-established findings among patients with schizophrenia (De Hert et al., 2006; Osby et al., 2000). Although antipsychotic agents have direct negative effects on some of these risk factors, most of them can be explained by their tendency to induce weight gain (De Hert et al., 2009). Weight gain has been observed in up to 30% of patients treated with second-generation antipsychotics, although the variation between these agents is considerable (Brandl et al., 2014). Clozapine and olanzapine are most often associated with weight gain (Newcomer, 2005; Leucht et al., 2013). Moreover, the highest rates of metabolic syndrome among patients on antipsychotic treatment are found in patients on clozapine (Eskelinen et al., 2015; Mitchell et al.,

2013).

Glucagon-like peptide-1 (GLP-1) is an endogenous peptide hormone secreted by enteroendocrine L-cells in the distal small bowel and colon (Drucker, 2006). It stimulates glucose-dependent insulin secretion in response to food intake (Iepsen et al., 2014). GLP-1 has also many other functions, such as regulation of satiety, inhibition of food intake, and inhibition of gastric emptying (Drucker, 2006). GLP-1 also induces reduction of body weight. It has major effects in several areas of the brain involved in appetite regulation (Heppner and Perez-Tilve, 2015). GLP-1 receptors are expressed in several tissues, including pancreas, gastrointestinal tract, kidney, lung, heart, and brain (Heppner and Perez-Tilve, 2015; Iepsen et al., 2014). Glucagon-like peptide-1 receptor (GLP-1R) agonism promotes weight loss and improves glucose homeostasis (Holst, 2007). Arcuate nucleus of the hypothalamus is a main site

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mediating the anorectic action of GLP-1 receptor (Secher et al., 2014). GLP-1R agonism interacts with leptin-dependent mechanisms. GLP-1R agonism preserves leptin levels, thereby mediating satiety and enhancing weight loss (Iepsen et al., 2015).

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) and pre-B cell colony-enhancing factor (PBEF), is an adipocytokine secreted by leucocytes, visceral adipose tissue adipocytes and macrophages, and several other cells and tissues such as skeletal muscle, liver, immune cells, cardiomyocytes and brain cells (Dahl et al., 2012; Friebe et al., 2011; Fukuhara et al., 2005). Increased plasma visfatin levels have been associated with overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases, low grade inflammation, and proinflammatory markers such as interleukin-6. However, the evidence so far is not consistent (Chang et al., 2011; Seo et al., 2008; Zhang et al., 2006). Moreover, polymorphisms in the NAMPT gene have also been associated with obesity, type 2 diabetes mellitus, lipid profile, proinflammatory status, and cardiovascular diseases (Belo et al., 2015; Blakemore et al., 2009; Javanmard et al., 2016; Motawi et al., 2014; Wang et al., 2011). Associations between circulating visfatin levels and antipsychotic treatment have been only little studied. Significant associations between antipsychotic-induced weight gain (AIWG) and visfatin levels have only been found in one study by Pisano et al., with lower levels of visfatin in the AIWG group than in untreated obese patients (Basoglu et al., 2010; Perez-Iglesias et al., 2008; Pisano et al., 2018).

The association between visfatin and GLP-1 is inconsistent. Bala et al. found that GLP-1 inhibits visfatin release from adipocytes. Moreover, both insulin and GLP-1 suppressed visfatin during an oral glucose load (Bala et al., 2011). However, GLP-1 has also been found to promote visfatin expression in adipocytes via protein kinase A pathway (Liu et al., 2013).

Clozapine and quetiapine have been found to impair glucose tolerance in rats via suppression of GLP-1 levels independent of insulin resistance caused by obesity (Smith et al., 2009). Moreover, clozapine may not have direct effects on glucose metabolism in the liver, but it stimulates insulin and glucagon secretion from the pancreas. In addition, glucagon like peptide-1 receptor agonist Boc5 was able to overcome the inhibitory effects of clozapine on glucose metabolism in isolated mouse islets. (Smith et al., 2014). GLP-1 secretion from intestinal L-cells is stimulated by muscarinic neurotransmission (Anini et al., 2002). The antimuscarinic properties of clozapine are well known. GLP-1 receptor agonists liraglutide and exenatide have been found to improve glucose tolerance, body weight, and cardiometabolic disturbances in patients with schizophrenia treated with clozapine or olanzapine (Larsen et al., 2017; Mayfield et al., 2016; Siskind et al., 2019). Moreover, GLP1R gene signaling has been suggested to have antipsychotic properties in animal models and to have an impact on glucose-dependent insulin release, satiety, memory, and learning in humans (Ramsey and Brennan, 2014).

There is a need for biomarkers for antipsychotic-induced weight gain, which would be sensitive to metabolic syndrome and disturbed food intake behaviors. GLP-1 and visfatin are linked with glucose metabolism and body weight regulation, and accordingly have associations with obesity-related comorbidity. Moreover, GLP-1 and visfatin are expressed both in central nervous system and periphery. This makes them promising candidates for a predictive biomarker of AIWG. However, associations between antipsychotic-induced weight gain and serum GLP-1 and visfatin levels have been little studied in patients with schizophrenia.

The aim of the present study was to test the possible role of serum GLP-1 and visfatin level alterations as markers of weight gain in association with other metabolic and inflammatory markers in patients with schizophrenia on clozapine treatment.

2. Materials and methods

2.1. Patients

The study was conducted in three hospital districts in Western Finland (Satakunta, Pirkanmaa, and Seinäjoki Hospital Districts). The patients were recruited at secondary inpatient and outpatient clinics and from sheltered accommodation units. The inclusion criteria for the study were: 1. Stabilized clozapine medication, and 2. Clinical diagnosis of F2 group according to ICD-10. The exclusion criteria were organic brain disease or other neurological disorder. The diagnosis was set by experienced psychiatrists in clinical settings. All patients completed a questionnaire eliciting, among others, weight and height, trend in weight change (marked increase, slight increase, no change, decrease), weight gain in kilograms during clozapine treatment, and smoking. Body mass index (BMI) was calculated using the weight and height information reported. Information on past medical history and duration of clozapine treatment was collected from the patient records. The study was approved by the local ethics committee. All patients gave informed consent on entry to the study and the approval applied to all three sites.

A descriptive analysis of the patient population has been reported earlier (Klemettilä et al., 2014). Of the 190 patients, 109 (57.4%) were male and 81 (42.6%) were female. Mean age was 43.1 years (range 20–67 years). The average time from the first hospital admission was 17.67 years (2–42 years). One hundred and eleven patients (58.4%) had been on clozapine treatment for more than five years, 60 patients (31.6%) from one to five years and four patients (2.1%) from three to twelve months. Those fifteen patients with no data on treatment duration available were recruited from long-term care units, and had all been on clozapine treatment for more than one year. One hundred and twenty-one patients (63.7%) were on clozapine monotherapy, and 69 (36.3%) had a combination therapy with other antipsychotics. Mean clozapine dose was 406 mg/day (100–800 mg/day). Mean BMI was 29.9 kg/m². One hundred and one patients (53.2%) were regular smokers, median 20 cigarettes per day. Smoking did not differ between genders, and was not associated with BMI. The baseline characteristics of the participants are presented in Table 1.

Table 1
Characteristics of the study cohort.

	Men (n = 109, 57.4%)	Women (n = 81, 42.6%)	Whole cohort (n = 190)
Age, mean (SD) years	43.0 (10.6)	43.3 (11.7)	43.1 (11.1)
Regular smoking, n (%)	60 (56.1%)	41 (50.6%)	101 (53.2%)
BMI, mean (SD) kg/m ²	29.0 (5.8)	31.2 (6.9)	29.9 (6.3)
Clozapine dose, mean (SD) mg	409 (147)	401 (153)	406 (149)
Clozapine combined with other antipsychotic medication, n (%)	38 (34.9%)	31 (38.3%)	69 (36.3%)
Patients who reported weight gain, n (%)	48 (44.0%)	53 (65.4%)	101 (53.2%)
GLP-1 serum concentration, mean (SD) pg/ml	167.2 (83.9)	144.2 (57.8)	157.2 (74.4)
Visfatin serum concentration, mean (SD) ng/ml	12.9 (13.3)	8.7 (5.7)	11.1 (10.9)
Insulin serum concentration, mean (SD) μU/ml	30.5 (34.8)	34.7 (36.5)	32.3 (35.5)
HOMA-IR, mean (SD)	9.1 (12.1)	11.5 (15.8)	10.1 (13.8)
Leptin serum concentration, mean (SD) pg/ml	13.5 (16.1)	47.9 (37.1)	28.1 (32.0)
Adiponectin serum concentration, mean (SD) pg/ml	2.91 (1.38)	3.76 (1.85)	3.27 (1.65)
HDL serum concentration, mean (SD) mmol/l	1.06 (0.29)	1.28 (0.37)	1.15 (0.34)
Triglycerides serum concentration, mean (SD) mmol/l	2.18 (1.17)	1.72 (0.93)	1.98 (1.09)
TNF-alfa serum concentration, mean (SD) pg/ml	2.81 (2.96)	2.50 (0.93)	2.68 (2.32)

2.2. Laboratory and clinical methods

For the laboratory analysis venous blood samples were collected after over-night fasting during a routine laboratory visit related to the clozapine treatment. Serum was separated and stored at -80°C until analyzed. Glucose, insulin, HDL-cholesterol, and triglycerides were measured with Cobas c6000 e601 (Roche Diagnostics) with detection limits of 0.11 mmol/l, 0.2 $\mu\text{U/ml}$, 0.08 mmol/l and 0.1 mmol/l, respectively. Levels of adiponectin, resistin, leptin, IL-1Ra, and TNF- α were measured by enzyme linked immunosorbent assay (ELISA) with the following reagents: DuoSet® ELISA (R&D Systems Europe Ltd, Abingdon, UK) for adiponectin, resistin and leptin, Quantikine® for IL-1Ra and Quantikine® HS for TNF- α (R&D Systems). Detection limits for adiponectin, resistin, leptin, and IL-1Ra were 15.6 pg/ml, and for TNF- α 0.5 pg/ml, respectively. Hs-CRP was measured using Tinaquant C-reactive protein (latex) high sensitive assay (Roche Diagnostics) with detection limits 0.05–10 mg/l. Serum levels of GLP-1 and visfatin were measured by enzyme linked immunosorbent assay (ELISA) with reagents from Merck Millipore (Billerica, MA, USA), and Phoenix Pharmaceuticals (Burlingame, CA, USA), respectively. The detection limit was 13.5 pg/ml for GLP-1 and 0.1 ng/ml for visfatin.

The descriptive analysis of HOMA-IR, HDL-cholesterol, triglycerides, adiponectin, leptin, IL-1Ra, hs-CRP, and resistin levels in this sample has been reported earlier (Klemettilä et al., 2014, 2015, 2017), Table 1.

Serum cytokine values (visfatin, $n = 6$; GLP-1, $n = 5$; IL-1Ra, $n = 3$; TNF- α , $n = 2$) missing due to limited amount of serum were excluded from the analysis.

2.3. Statistical analyses

Comparison of means between genders was analyzed with two-tailed t-tests. Pearson's correlation and Spearman's rho were used to analyze the associations between clinical markers. Distributions of each variable were checked manually to control for possible technical errors in laboratory assays. The statistical significance of correlations between levels of serum GLP-1 and visfatin, and BMI, HOMA-IR, lipids, and cytokines/adipokines was set at $p = 0.006$ using Bonferroni correction by dividing the significance level of $p = 0.05$ by the number of markers analyzed. In all other statistical analyses the level of significance was $p < 0.05$. Due to the asymmetric distribution of levels of GLP-1, visfatin, triglycerides, HOMA-IR, IL-1Ra, TNF- α , and hs-CRP, logarithmic transformation of these markers was used in the bivariate analysis of correlations and groupwise associations. The data analysis was carried out using SPSS/Win software (version 19.0, SPSS inc., Chicago, IL, USA).

3. Results

Mean (SD) serum concentration of GLP-1 among these patients was 157.2 (74.4) pg/ml. In men vs. women the mean (SD) GLP-1 serum concentrations were 167.2 (83.9) vs. 144.2 (57.8) pg/ml with no statistical significance.

Mean (SD) serum concentration of serum visfatin was 11.1 (10.9) ng/ml. Serum concentrations of serum visfatin differed between genders. Mean (SD) serum visfatin levels were 12.9 (13.3) vs. 8.7 (5.7) ng/ml ($\log\text{Visf } p = 0.013$) in men vs. women, Table 1.

The correlations between serum GLP-1 levels and other markers are presented in Table 2. Levels of serum GLP-1 correlated significantly in the whole patient sample with serum levels of insulin ($r = 0.25$, $p = 0.001$), and with HOMA-IR ($r = 0.30$, $p < 0.001$).

Among men serum GLP-1 levels correlated significantly with serum levels of visfatin ($r = 0.33$, $p = 0.001$), leptin ($r = 0.32$, $p = 0.001$), and insulin ($r = 0.37$, $p < 0.001$), and with HOMA-IR ($r = 0.42$, $p < 0.001$) and BMI ($r = 0.34$, $p < 0.001$). The correlations of GLP-1 levels among women were with visfatin ($r = -0.12$, $p = 0.28$), leptin ($r = -0.11$, $p = 0.34$), insulin ($r = 0.09$, $p = 0.43$), HOMA-IR ($r = 0.16$, $p = 0.17$), and BMI ($r = -0.14$, $p = 0.25$). Among men serum GLP-1 levels were

Table 2

Pearson's correlations (r) between GLP-1 and visfatin, leptin, insulin, HOMA-IR, and BMI.

	GLP-1 Men	Women	Whole cohort
Visfatin	0.33 ($p = 0.001$)	-0.12 ($p = 0.28$)	0.22 ($p = 0.0032$)
Leptin	0.32 ($p = 0.001$)	-0.11 ($p = 0.34$)	-0.0069 ($p = 0.93$)
Insulin	0.37 ($p < 0.001$)	0.09 ($p = 0.43$)	0.25 ($p = 0.001$)
HOMA-IR	0.42 ($p < 0.001$)	0.16 ($p = 0.17$)	0.30 ($p < 0.001$)
BMI	0.34 ($p < 0.001$)	-0.14 ($p = 0.25$)	0.12 ($p = 0.12$)

associated with reported weight change during clozapine treatment ($\rho = 0.28$, $p = 0.005$), while in women they were not ($\rho = 0.04$, $p = 0.75$), Fig. 1.

Serum visfatin levels correlated significantly with levels of serum GLP-1 ($r = 0.33$, $p = 0.001$) and insulin ($r = 0.30$, $p = 0.002$) among men.

4. Discussion

This is the largest study so far on GLP-1 and visfatin serum levels in patients with schizophrenia, especially in patients on clozapine treatment (Bocchio-Chiavetto et al., 2018).

There was a significant correlation between serum GLP-1 levels and levels of insulin and HOMA-IR as expected. However, gender difference was found in associations between GLP-1 and levels of visfatin, leptin, insulin, HOMA-IR, BMI, and weight change with significant correlations among men only. In general, fasting and post-prandial levels of GLP-1 have been found to be lower in patients with type 2 diabetes mellitus than among healthy subjects (Lastya et al., 2014). The present women had more weight gain and were more obese than the men and also had higher levels of leptin (Klemettilä et al., 2015). It can be presumed, that women may be more sensitive to the suppressive effects of clozapine on GLP-1 secretion, whereas the hormonal response in men may compensate more for the metabolic adverse effects of clozapine via elevated GLP-1 levels.

Visfatin levels have not generally been found to differ between first episode psychosis, long-term schizophrenia and matched control groups (Bocchio-Chiavetto et al., 2018; Sahpolat et al., 2020). In the present patients serum visfatin levels were higher in men than in women. Visfatin is secreted mainly in visceral adipose tissue, and visfatin levels have been reported to correlate with visceral fat mass (Fukuhara et al., 2005). Visceral adiposity is typical for male obesity. In the study by Sitticharoon et al. (2014) serum visfatin was associated with weight gain in a non-psychiatric population (Sitticharoon et al., 2014). In the present patient sample the most obese subjects, both men and women, were those who had gained weight during clozapine treatment (Klemettilä et al., 2015). However, no associations between serum visfatin levels and BMI or weight change were found in the present patients. The association between visfatin and obesity is somewhat controversial. Visfatin is secreted by several cells and tissues with leucocytes being a major source of visfatin, and may be predominantly associated with inflammatory state rather than directly with BMI (Friebe et al., 2011).

There are certain limitations in the study. The study was cross-sectional, and the clinical data were collected retrospectively. Weight change was self-reported. Moreover, a healthy control population for visfatin and GLP-1 levels would have enhanced the reliability of the results. Combination therapy with other antipsychotics with different side-effect and receptor profiles in one third of the patients may also be a confounding factor. Due to lack of data on waist circumference, it was not possible to reliably identify patients with central obesity. However, this sample can be considered homogenous and representative of the group of patients with long-term schizophrenia on clozapine treatment.

In conclusion, high serum GLP-1 level seems to be a marker of metabolic risk factors among male patients. GLP-1 could serve as a possible clinical marker for clozapine-induced weight gain. Women

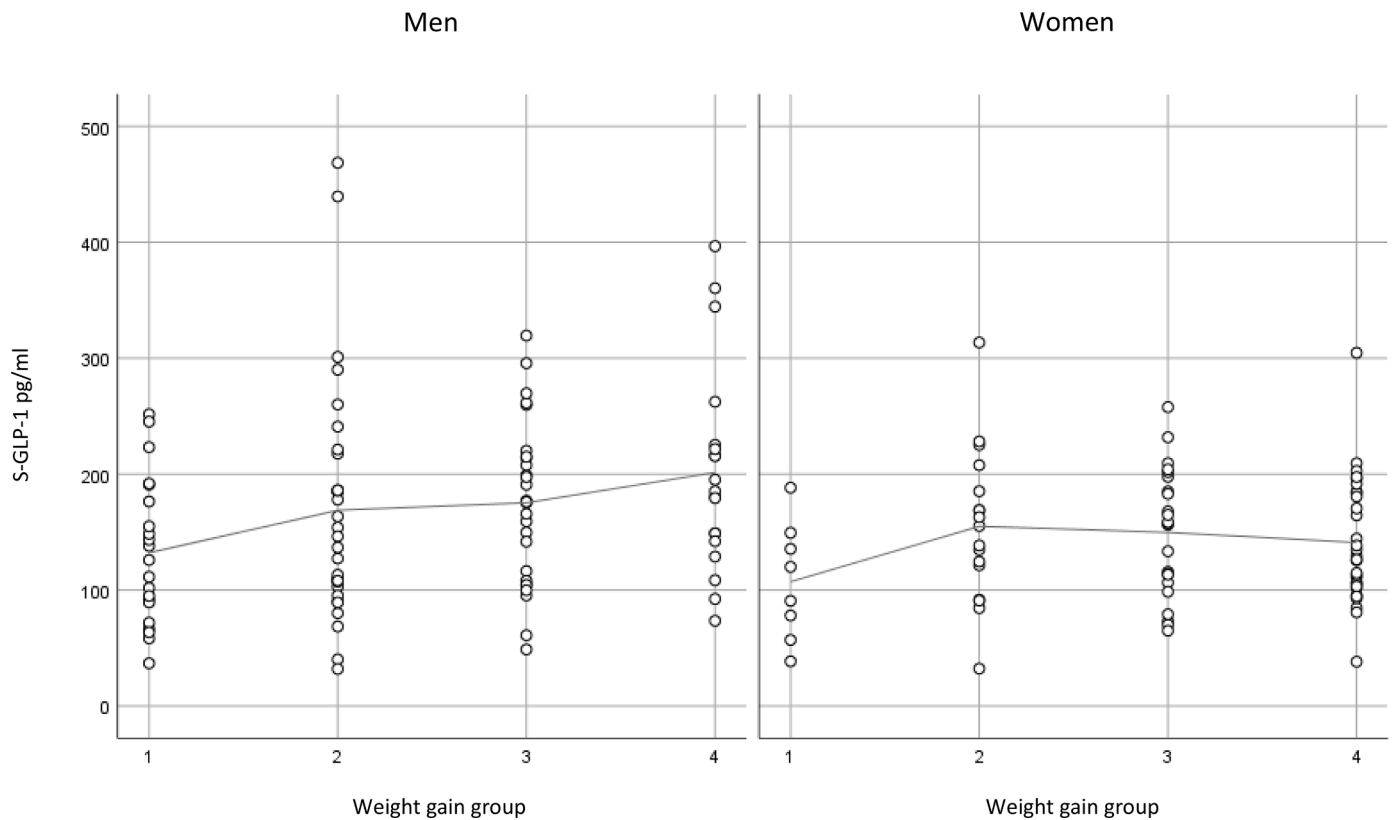


Fig. 1. Scatters between serum GLP-1 levels and weight change (decrease, no change, slight increase, marked increase, 1–4 respectively) in men and women.

seem to be at greater risk of clozapine-induced metabolic adverse effects. Patients on clozapine would benefit from GLP-1 agonists as preventive treatment. Serum visfatin does not seem to be a feasible marker of weight gain or metabolic comorbidity in association with clozapine treatment. Longitudinal studies are needed to clarify the mechanisms and directions of these interactions.

5. Authors contributions

J.-P. Klemettilä (first author and corresponding author) wrote the manuscript. A. Solismaa did the data management. O. Kampman conducted the statistical planning and analyses. E. Leinonen, O. Kampman and N. Seppälä did the patient recruitment. M. Hämäläinen and E. Moilanen conducted the laboratory analyses. O. Kampman made substantial comments and edited the manuscript. All authors contributed to commenting and editing the final version of the manuscript.

Declaration of Competing Interest

J.-P.K. has served on a national advisory board of Lundbeck, received speaker's fee from Otsuka and received support from Lundbeck to participate in an international congress. A.S. has no conflicts of interest to declare. O.K. has no conflicts of interest to declare. N.S. is a part-time consultant and has received speaker's fees from Mylan and Viatrix Finland. He has also served on a national advisory board of Janssen-Cilag, Finland and Recordati, Sweden and as a specialist panel member of Meda Italy. E.L. has no conflicts of interest to declare.

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