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ORIGINAL PAPER

Glucose homeostasis in major depression and schizophrenia: a comparison among drug-naïve first-episode patients

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Abstract
There is evidence for insulin resistance in drug-naïve first-episode schizophrenia (Sz) patients. We have tested whether impaired insulin homeostasis is also present in first-episode patients with major depression (MD) and if this can be discerned from stress-related and medication effects. Homeostatic model assessment of insulin resistance (HOMA-IR) was determined in a cross-sectional cohort study of acute first-episode drug-naïve patients with MD ($n=18$) or Sz ($n=24$), and healthy controls (C, $n=43$). Morning cortisol and catecholamine metabolites were assessed to control for hormonal stress axis activation. Subjects were matched for sex, age, body mass index and waist–hip ratio to exclude the possibility that overweight and visceral adiposity were potential confounding factors. HOMA-IR did not differ between MD and controls, but was increased in Sz compared to MD ($p=0.002$) and controls ($p=0.012$). Catecholamine metabolites were elevated in both patient groups, indicating presence of hormonal stress axis activation. However, diagnosis-related changes of HOMA-IR were independent from this. Impaired insulin sensitivity was absent in MD, but specifically related to the early disease course of Sz. Thus, considering previous studies in this field, MD may be related to impaired glucose/insulin homeostasis in the long-term but not in early disease stages.

Keywords Glucose · Insulin · Major depression · Schizophrenia · Stress

Introduction

Major depression (MD) may predispose to the development of type 2 diabetes. For instance, the relative incidence risk rate for type 2 diabetes was increased to 1.60 within a 3–16 year follow-up in a longitudinal study on depression [9]. Likewise, type 2 diabetes and prediabetes were significantly associated with depression in a cross-sectional study [10]. It is known that tricyclic antidepressants, mirtazapine and mood stabilizers such as lithium and valproate are associated with weight gain and reduced insulin sensitivity, while selective serotonin reuptake inhibitors (SSRIs) and the dual mechanism serotonin–noradrenalin reuptake inhibitors (SNRIs) do not disrupt glucose homeostatic dynamics [8]. Several studies have described insulin resistance in patients with MD, but these patients had been medicated or were

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off medication for only 1–2 weeks [4, 6, 11, 17–19]. Thus, medication effects cannot be ruled out as a confounding factor and it is still unclear if an altered glucose metabolism is a disease-inherent factor of MD.

Impaired glucose metabolism and development of metabolic syndrome have also been observed in schizophrenia (Sz), contributing to a reduced average life expectancy [15]. As a consequence of impaired cerebral insulin signaling, neural glucose uptake and utilization may be altered, as suggested by cerebrospinal fluid analyses [3]. It has been assumed that this association is caused by side effects of atypical antipsychotic drugs like clozapine and olanzapine [7]. However, a recent meta-analysis by Pillinger et al. found convincing evidence for impaired fasting glucose tolerance already in drug-naïve first-episode Sz patients [12]. Thus, impaired insulin homeostasis appears to occur early during the disease course of Sz independent from medication.

Aims of the study

To test whether or not similar changes regarding insulin sensitivity are also present during the early disease course of MD, homeostatic model assessment of insulin resistance (HOMA-IR) and stress hormone levels were determined for acutely ill drug-naïve patients with MD compared to healthy controls and patients with Sz. Our focus on drug-naïve patients aimed to exclude side effects of medication as a potential confounding factor. In addition, we controlled for hormonal stress activation, since cortisol and catecholamines are catabolic and functional antagonists of insulin.

Materials and methods

Study design

The study was performed in accordance with German laws, the 1964 Declaration of Helsinki and its later amendments, and the guidelines of the local institutional review board. Written informed consent was obtained from all the participants. Blood samples were retrieved from the scientific blood bank at Magdeburg's University Department of Psychiatry. The tested samples were collected during the time period February 2008 to March 2010 from all available sequentially admitted acutely ill drug-naïve inpatients with MD ($n=18$). This cohort was compared to healthy controls (see below) and Sz patients from the same collection period ($n=24$) [14]. Longitudinal samples after 6 weeks of treatment were available from 14 MD cases (mirtazapine $n=6$, venlafaxine $n=8$). Psychopathology was monitored using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Scale (HAMD-21).

Controls (C, $n=43$; healthy blood donors, hospital staff and their relatives) were matched for sex, body mass index (BMI), and waist–hip ratio (Table 1). As expected, drug-naïve patients with MD tended to be older than the drug-naïve Sz cohort (MD vs. Sz: $p=0.086$). Patients smoked

Table 1 Demographic data and clinical scores

	C ($n=43$)	MD ($n=18$)	Sz ($n=24$)	C vs. MD vs. Sz[a]	C vs. MD[b]	C vs. Sz[b]	MD vs. Sz[b]
Age (years)	35.00 (26.00, 45.00)	46.00 (33.50, 52.75)	31.00 (25.00, 37.50)	0.053	0.249	0.249	0.086
Sex (male/female)	26/17	11/7	13/11	0.878[c]	1.000[c]	0.797[c]	0.757[c]
Body mass index (kg/m^2)	24.38 (21.80, 27.83)	24.51 (21.46, 26.36)	22.15 (21.02, 27.40)	0.518	1.000	0.765	1.000
Waist–hip ratio (cm/cm)	0.87 (0.81, 0.93)	0.88 (0.84, 0.99)	0.87 (0.82, 0.91)	0.636	1.000	1.000	1.000
Smoking (cigarettes/day)	0.00 (0.00, 4.00)	10.00 (0.00, 17.75)	10.00 (0.25, 17.00)	**0.002**	**0.013**	**0.004**	1.000
Corrected PANSS-P score	NA	NA	17.0 (12.5, 19.2)	NA	NA	NA	NA
Corrected PANSS-N score	NA	NA	9.5 (4.5, 19.8)	NA	NA	NA	NA
Corrected PANSS-G score	NA	NA	24.5 (22.8, 34.2)	NA	NA	NA	NA
Corrected PANSS-sum score	NA	NA	55.0 (44.0, 68.2)	NA	NA	NA	NA
HAMD-21-sum score	NA	21.0 (15.8, 24.3)	NA	NA	NA	NA	NA

Data are presented as median, quartile 1, and quartile 3; significant p values are displayed in bold letters

C controls, *HAMD-21* Hamilton depression scale, *MD* major depression cohort, *corrected PANSS scores*, i.e., subtraction of minimum scores representing 'no symptoms' from the Positive and Negative Syndrome Scale (PANSS) scores, *Sz* schizophrenia cohort, *NA* not applicable

[a]Kruskal–Wallis/*H*-test, [b]Mann–Whitney/*U*-test, exception: [c]Fisher's exact test

more cigarettes than controls (Sz vs. C: $p=0.004$; MD vs. C: $p=0.013$).

Prior to definite inclusion of the blood samples into our scientific blood bank, psychosis or depression resulting from other medical conditions and substance-induced psychosis were excluded by a thorough physical examination, routine blood analysis, and screening for illegal drugs. The same tests were carried out for the controls. Controls were screened for personal or family history of neuropsychiatric disorders using the Mini-International Neuropsychiatric Interview [13]. Exclusion criteria consisted of the presence of immune diseases, immunomodulating treatment, cancer, chronic terminal disease, cardiovascular disorders, manifest diabetes or severe trauma.

Blood samples were obtained from fasting subjects at 8:00 a.m. and collected into BD Vacutainer™ tubes (Becton Dickinson; Heidelberg, Germany). Plasma tubes were centrifuged immediately at 1000*g* for 10 min; supernatants were stored at − 80 °C. Serum tubes were processed as above for plasma after 2 h clotting. Morning urine was sampled, acidified (pH 2–4) and stored at − 80 °C.

Biochemical analyses

Insulin levels were determined using a radioimmunoassay (BI-Insulin IRMA; CIS BIO GmbH; Berlin, Germany). Plasma glucose levels were analyzed by a commercial enzymatic method (GOD, Roche Diagnostics, Germany). HOMA-IR was calculated using the formula "[insulin (mU/L) × glucose (mmol/L)]/22.5". Total serum cortisol levels were measured using the Immulite 2000 system (Siemens Healthcare Diagnostics; Eschborn, Germany), which is a fully automatic random access chemiluminescence-enhanced enzyme immunoassay protocol.

Urinary levels of the catecholamine metabolites metanephrine and normetanephrine were measured as previously described using a commercially available high performance liquid chromatography (HPLC) method with electrochemical detection (Chromsystems Instruments & Chemicals GmbH; Munich, Germany) [5]. An internal standard (3-hydroxy-2-methylbutanoic acid) was used as a reference to estimate both analyte concentrations. The ratio of metanephrines to creatinine for each urine sample was calculated to correct for internal dilution. Measurement of creatinine was carried out using standard methods on the Modular platform (Roche Diagnostics, Penzberg, Germany).

Statistics

Fisher's exact tests were performed to calculate group differences regarding gender. Most data were not normally distributed, as indicated by Shapiro–Wilk tests. Thus, non-parametric analyses were applied. The demographic variables age, BMI, waist–hip ratio, and smoking were compared by Kruskal–Wallis *H*-tests and post hoc Mann–Whitney *U*-tests corrected by the Bonferoni–Holm method.

HOMA-IR was the parameter of interest. Potential associations of HOMA-IR with other parameters (age, BMI, waist–hip ratio, cortisol, metanephrine, normetanephrine levels or smoking) were determined using Spearman's rank correlation testing. Only BMI was significantly correlated with HOMA-IR ($r=0.324$, $p=0.003$). Therefore, analysis of covariance using aligned rank transformation of data (ART; http://www.r-project.org) including BMI as single covariate was applied to determine diagnosis-related differences of HOMA-IR. Repeated measures ART was used to calculate longitudinal changes of HOMA-IR in MD. All statistical tests were two-tailed and $p<0.05$ was considered significant.

Results

ART including BMI as covariate revealed diagnosis-related differences of HOMA-IR (Fig. 1; $F=5.360$, $p=0.006$) between MD [median (quartile 1, quartile 3): 0.45 (0.33, 0.62) mU mmol/L], Sz [0.72 (0.38, 2.28) mU mmol/L], and controls [0.56 (0.36, 0.85) mU mmol/L]. Post hoc ART analyses revealed no significant difference between MD and controls ($F=2.638$, $p=0.109$), but a higher HOMA-IR in Sz vs. MD ($F=10.768$, $p=0.002$) and in Sz vs. controls ($F=6.677$, $p=0.012$). Overall, HOMA-IR did not change significantly in MD after 6 weeks of treatment ($F=0.167$, $p=0.689$), but type of treatment interacted with

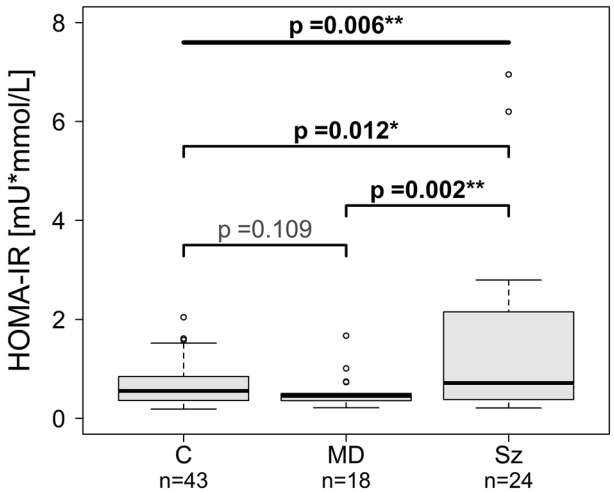

Fig. 1 Diagnosis-dependent distribution of HOMA-IR. *C* controls, *MD* major depression cohort, *Sz* schizophrenia cohort, *HOMA-IR* homeostatic model assessment (HOMA) of insulin resistance = [insulin [mU/L] glucose [mmol/L)]/22.5. Box plots show the median, interquartile range, sample minimum and sample maximum, outliers are displayed as circles, $^{*}p<0.05$, $^{**}p<0.01$

delta-HOMA-IR [$F = 7.334$, $p = 0.018$; delta-HOMA-IR: + 0.35 (0.10, 1.04) mU mmol/L in mirtazapine- versus − 0.04 (− 0.33, 0.20) mU mmol/L in venlafaxine-treated patients].

Cortisol was non-significantly elevated in MD ($p = 0.105$) and Sz ($p = 0.125$) versus controls [MD: 296 (178, 750) µgU/L, Sz: 266 (177, 403) µgU/L, controls: 218 (173, 252) µgU/L]. Metanephrine concentrations were significantly increased in MD ($p = 0.008$) and Sz ($p = 0.008$) compared to controls [MD: 77.1 (46.4, 121.1) µg/g creatinine, Sz: 71.5 (42.9, 127.1) µg/g creatinine, controls: 40.0 (27.8, 61.0) µg/g creatinine]. Similarly, normetanephrine concentrations were significantly higher in MD ($p = 0.007$) and Sz ($p = 0.028$) versus controls [MD: 162.5 (101.1, 237.3) µg/g creatinine, Sz: 147.7 (89.1, 217.7) µg/g creatinine, controls: 89.07 (51.8, 140.9) µg/g creatinine].

HOMA-IR correlated with BMI ($r = 0.324$, $p = 0.003$), but not with age ($r = 0.117$, $p = 0.289$), levels of cortisol ($r = 0.034$, $p = 0.759$), metanephrine (r=-0.064, $p = 0.564$), normetanephrine ($r = -0.024$, $p = 0.826$), or smoking ($r = -0.015$, $p = 0.892$). HOMA-IR was not related to HAMD-21 sum ($r = -0.253$, $p = 0.326$) or corrected PANSS-P ($r = 0.086$, $p = 0.690$), PANSS-N ($r = 0.099$, $p = 0.647$), PANSS-G ($r = -0.183$, $p = 0.393$) and PANSS-sum ($r = 0.000$, $p = 0.999$) scores.

Discussion

Our results support the recently raised notion of impaired insulin/glucose homeostasis in drug-naïve Sz patients [12], small sample size notwithstanding. The patient and control groups were well-matched for sex, age, BMI and waist–hip ratio to rule out the possibility that overweight or visceral adiposity could be factors explaining altered HOMA-IR scores. While lifestyle factors such as exercise, sedentary behavior and diet were not examined in this study, HOMA-IR was not related to smoking. These metabolic effects appear to be related to Sz itself, rather than merely being a side effect or consequence of antipsychotic treatment, hormonal stress axis activation, or body fat composition.

Our negative finding in drug-naïve MD patients implies that impaired insulin sensitivity appears to be specifically related to Sz and not to psychiatric diseases in general. At a first glance, this may be an unexpected finding, because of the previously described association of type 2 diabetes and prediabetes with depression [9, 10]. However, there are still some controversies, since undiagnosed diabetes was not associated with depression [10] and Mendelian association studies observed no genetic correlation between type 2 diabetes and MD [2]. Thus, factors other than the disease itself, like chronic hormonal stress axis activation, lifestyle factors (e.g., sedentary lifestyle and unhealthy diet), and side effects of medication may be responsible for the manifestation of type 2 diabetes in MD.

Antidepressant drugs like mirtazapine, are associated with weight gain and reduced insulin sensitivity, while selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenalin reuptake inhibitors (SNRIs) do not disrupt glucose homeostatic dynamics [8]. Accordingly, we observed a divergent change of HOMA-IR after 6 weeks of treatment with mirtazapine vs. venlafaxine. Several previous studies have described insulin resistance in chronically ill patients with MD or after a relatively short medication washout phase of 1–2 weeks [4, 6, 11, 17–19]. To our knowledge, only two studies have analyzed HOMA-IR in drug-naïve MD patients so far. Vareka et al. described an increased HOMA-IR in MD patients compared to controls [16]. These patients were relatively old (~ 60 years), and somatic or organic brain disorders were not excluded and may, therefore, have confounded the results. Moreover, it is unclear whether the subjects fasted, since both patients and controls had a mean HOMA-IR above 2.5, suggesting clinically relevant insulin resistance. Only Chang et al. analyzed HOMA-IR in fasting drug-naïve MD patients with a mean age comparable to that in our study and found no insulin resistance [1].

In conclusion, in contrast to Sz, MD is likely to be related to impaired glucose/insulin homeostasis in the long-term but not in the early disease stage. Furthermore, the impairments may not be attributable to the disease itself, but rather to medication or other secondary effects such as changes in lifestyle. Larger future studies should aim to clarify the pathophysiological significance of these results and if these findings from rather small cohorts can be generalized. The HOMA-IR is widely used to measure insulin sensitivity and is considered robust for epidemiologic purposes. However, more specific measures such as the glucose clamp technique will have to be applied in drug-naïve patients with Sz and MD to characterize in more detail how well these individuals metabolize glucose or how sensitive they respond to insulin. A better understanding of the underlying mechanisms related to glucose metabolism in Sz and MD may provide insights regarding novel therapeutic approaches.

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Compliance with ethical standards

Conflict of interest Dr Sarnyai has been a speaker for Otsuka and Lundbeck. No other disclosures were reported.

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