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ABBREVIATIONS

ABTS*+	2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical
AC(s)	acylcarnitine(s)
AODS	antioxidant defense system
BMI	body mass index
C4DC	carnitine – C4-dicarboxylcarnitine
CARN	carnitine
CAT	catalase
CK(s)	cytokine(s)
CoA	coenzyme-A
COX-1	cyclooxygenase 1
COX-2	cyclooxygenase 2
CPT-1	palmitoyltransferase 1
CrAT	carnitine acetyl-CoA transferase
CRP	C-reactive protein
CS(s)	control subject(s)
FA	fatty acid
FAO	fatty acid oxidation
FEP	first-episode psychosis
FEPa	first-episode psychosis patients after treatment
FEPb	first-episode psychosis patients at the baseline (before treatment)
GLM	general linear model
Gpx	glutathione peroxidase
GSH	reduced glutathione
GSSG	oxidized glutathione
H_2O_2	hydrogen peroxide
HbA1c	glycated hemoglobin
ICD-10	International Classification of Diseases, Tenth Edition
IFN(s)	interferon(s)
IFN-γ	interferon gamma
IgE	immunoglobulin E
IL(s)	interleukin(s)
LCAC(s)	long-chain acylcarnitine(s)
LOD	level of detection
MDA	malondialdehyde
Met	methionine
Met-SO	methionine sulfoxide, oxidized methionine
MHC	major histocompatibility complex
MitoDys	mitochondrial dysfunction
NK	natural killer
NO	nitric oxide
O2•−	superoxide radical
OH•	hydroxyl radical
ONOO•	peroxinitrite

OSI	oxidative stress index
OxS	oxidative stress
PAI-1	plasminogen activator inhibitor-1
PANSS	Positive and Negative Syndrome Scale
PLA2	phospholipase A2
PON1	paraoxonase 1
RBC	red blood cell
RNS	reactive nitrogen species
RO	lipid alkoxyl radical
ROO	lipid peroxyl radical
ROOH	lipid hydroperoxide
ROS	reactive oxygen species
RS	reactive species
SCAC(s)	short-chain acylcarnitine(s)
SCZ	schizophrenia
sIL-2R	soluble interleukin 2 receptor
SOD	super oxide dismutase
TAC	total antioxidative capacity
TAS	total antioxidant status
TBARS	thiobarbituric acid reactive substances
TCA	tricarboxylic acid cycle
TGF(s)	transforming growth factor(s)
TGF-β	transforming growth factor beta
TNF(s)	tumor necrosis factor(s)
TNF-α	tumor necrosis factor alpha
TPX	total peroxide
TRAP	total radical-trapping antioxidant parameter

1. INTRODUCTION

Schizophrenia (SCZ) has long been a part of human history, but as a discrete mental illness SCZ was first described in 1887 by the German physician Emil Kraepelin, who used the term "dementia praecox" (early dementia) and believed that this was primarily a disease of the brain and specifically a form of dementia. The term for schizophrenia is slightly over 100 years old, when the Swiss psychiatrist Eugen Bleuler introduced it for the first time in 1911, being also the first to describe "positive" and "negative" symptoms. Since then, the definition of SCZ has continued to evolve and nowadays it includes broader symptom classes which are most commonly referred to as positive, negative, cognitive and affective symptoms; however, to date, the diagnosis of the disease is still based mainly on personal and thus subjective interviews and identification of symptom clusters by a psychiatrist.

SCZ is a chronic form of psychotic illness that starts with first-episode psychosis (FEP) which requires rapid medical intervention and is considered an important diagnostic pillar of this mental illness. Psychosis is a complex of symptoms accompanying SCZ that includes symptoms such as disorganized thought, speech and behaviour, psychomotor retardation and/or agitation. The onset of psychosis is usually preceded by many years of different underlying biological processes (Kahn & Sommer 2015) resulting among others in an increased pro-inflammatory and pro-oxidative status (Song *et al.* 2009; Girgis *et al.* 2014). The roots of metabolomic imbalance are still being studied, but increasingly more scientists agree on the fact that the imbalance contributing to psychosis is present before the onset of first psychotic episode and the start of pharmacological treatment (Song *et al.* 2014).

Metabolomics is a large-scale study of low molecular weight metabolites within cells or biofluids that reflect the underlying biochemical activity and state of cell/tissue, biological fluid, organ or organism in general. Metabolomics provides an integrated picture of genomic, transcriptomic and proteomic variation in accordance with physiological and environmental factors that together reflect the functional status of individuals. Quantifiable differences in metabolite patterns provide valuable hints for understanding the mechanism of the disease and for developing diagnostic biomarkers for mental disorders (Quinones & Kaddurah-Daouk 2009).

Metabolomic studies in SCZ patients have identified disturbances of several metabolic pathways, such as glycose, lipid, amino acid metabolism and imbalance redox status (Bitanihirwe & Woo 2011; Wu *et al.* 2013; Lee *et al.* 2011). The latter is closely linked to a variety of pathophysiological processes, such as inflammation, lipid peroxidation, mitochondrial dysfunction, etc., leading to an altered homeostasis and metabolic syndrome. The finding that metabolic disorder is interconnected with low-grade systemic inflammation which, in turn, is closely related to oxidative stress (OxS), has given ground for the research that resulted in the current thesis. Multiple studies have been formerly carried out on patients with chronic SCZ but metabolomic data available on antipsychotic-

naïve FEP patients as they go through their first psychotic episode are limited and often contradictory. Metabolomic profiling of drug-naïve FEP patients may give valuable information by enabling exclusion of the effects of treatment and examination of shifts in metabolite levels during the first course of antipsychotic treatment.

Currently, both clinical studies and treatment strategies are aimed to target the early prevention and intervention in psychotic conditions, allowing to anticipate better recovery and providing a more hopeful view on the prognosis for early treated patients. However, one of the obstacles so far has been the relatively subjective diagnostic modality that may result in a considerable error rate due to the complex spectrum of symptoms and their similarity to symptoms of several mental disorders (Keller *et al*. 2011). In the light of these facts, it is relevant to explore the molecular mechanism and to develop objective diagnostic biomarkers for SCZ, which would not only improve our understanding of the disease but would also enable to diagnose the disease in its early stage and lead to efficient and specific therapies. Therefore, the current thesis was aimed to obtain information about lipidomics, inflammation and OxS status in FEP patients and to compare changes in the metabolomic status within the FEP patients' group before and after seven-month antipsychotic treatment.

2. REVIEW OF LITERATURE

2.1. General overview of schizophrenia

SCZ is a complex, heterogeneous and severe psychiatric illness affecting about 1% of the population (National Institute of Mental Health- NIMH 2015) and is considered one of the top 15 leading causes of disability worldwide (Steel 2016). SCZ includes distinct (but often co-existing) symptom classes within the same person at different phases of the illness, which are commonly referred to as:

- Positive symptoms that contain perceptual disturbances of reality, such as hallucinations (including visual and auditory, as well as other sensory perceptions without any real stimulus), delusions (false beliefs with strong conviction), thought disorders (such as bizarre thoughts, suspiciousness and paranoia), movement disorders (catatonia or agitated body movements) and disorganized thoughts, speech and behaviour,
- Negative symptoms that include social and emotional withdrawal from every-day life, low energy, apathy and anhedonia, poor self-care, absent or blunted or incongruous emotional responses, lethargy and lack of interest in activities and people,
- Affective or mood symptoms – e.g. symptoms of mania, depression, mood swings, suicidal thoughts or behaviour, anxiety, guilt, irritability, and
- Cognitive symptoms that are typically characterized by prominent specific deficits in memory and learning, in working memory (handling of new and stored information), in executive functions (planning, decision making, reasoning and problem solving and flexible shifting of goals), attention, processing speed, and social cognition which are evident on a background of a generalized cognitive deficit (Dickinson *et al.* 2008; Tandon *et al.* 2009; Howes & Kapur 2014; Millan *et al.* 2016).

From the clinical and research aspect of the disease, it is reasonable to differentiate between prodromal phase, FEP and chronic phase of SCZ.

2.1.1. Prodromal phase of schizophrenia

Typically, the prodrome is characterised by nonspecific sleep disruption, mood and anxiety disorder symptoms, negative symptoms, attenuated positive symptoms and/or brief self-limiting psychotic symptoms, as well as cognitive dysfunctionality (Yung *et al*. 1996; Yung & McGorry 1996; Fusar-Poli *et al*. 2014; Kahn & Sommer 2015; Conus 2010; Millan *et al*. 2016). Velthorst *et al*. (2013) indicate that chronic low functioning due to psychosocial stressors, lack of social support, maladaptive adaption skills and/or another mental disorder, such as depression may be an indicator of upcoming SCZ-spectrum disorder and can contribute to the onset of psychosis in a vulnerable person. Notable

deterioration in social and occupational functioning is definitely part of the prodromal phase of SCZ. When evaluating the prodromal period in terms of the risk for psychotic disorder, it appears that in general about one third of ultra-high risk cases convert to psychosis, about one third do not develop but remain symptomatic with functional impairment and about one third recover functionally and symptomatically (Gee & Cannon 2011). Häfner and Maurer *et al.* (1995) have identified two stages in the early course of the disease that are relevant for identifying the risk and providing intervention: a) pre-psychotic prodromal stage, from the first sign of the illness to the first psychotic symptom, with an average duration of 4.8 years (median 2.33 years); b) psychotic pre-phase, from the first positive symptom to the first admission, with an average duration of 1.3 years (median 0.8 years).

2.1.2. First-episode psychosis

Approximately 15% of patients with SCZ and other psychoses experience their FEP before the age of 18 (Amminger *et al.* 2011), but it is most commonly experienced around 18–35 years of age (Davies *et al.* 2017). Early onset of the disease can cause more developmental impairment, show greater severity of negative symptoms and increase the risk of some negative results compared to patients with delayed onset (Ballageer *et al.* 2005; Joa *et al.* 2009; Diaz-Caneja *et al.* 2015).

Psychosis includes a set of clinical signs associated to positive symptomatology of SCZ: hallucinations and delusions; detachment from reality; psychomotor anomalies, such as catatonia or agitation; compromised insight, and disorganized thinking, speech and behaviour. Psychosis is generally used as the operational definition of transition to SCZ-spectrum disorders, despite its less systematic occurrence in other disorders (Millan *et al.* 2016). According to Millan *et al*. (2016), full-blown positive symptoms during the first episode of psychosis are considered the diagnostic pillar of SCZ.

Breitborde *et al.* (2009) have clarified the operational definition of FEP through three main categories: (i) identification of the first (antipsychotic) treatment contact; (ii) establishment of the duration of antipsychotic medication use; and (iii) identification of the duration of psychosis. Although there is no complete consensus on this definition, it allows harmonizing the concept of this stage of schizophrenia spectrum disorders and adjusting the subset of patients for clinical research.

Studying of FEP patients enables exclusion of the effects of psychotropic medications and acquisition of more information on the pathogenetic mechanisms of the disease since FEP is associated with important changes in the structure and functioning of the brain. The way FEP is managed and treated may play an important role in the clinical presentation and outcome of the disease course. Therefore, the current thesis is focused on patients with FEP.

2.1.3. Chronic phase of schizophrenia

With the exception of a minority of patients who only suffer one psychotic episode, those with chronic SCZ will be at risk of psychotic crises throughout their lives (Millan *et al.* 2016). The results of longitudinal studies indicate that about one third of patients will have experienced a relapse within one year after recovery and two thirds of the remaining patients before two years. Seventy to eighty percent of patients experience relapses within three to five years (Linszen *et al.* 2001). There is some evidence that with recurrent episodes of psychosis, the time to obtain response increases and the proportion of patients achieving remission decreases. Psychotic relapse and incomplete recovery are factors leading to the chronic phase of the disease (Pawełczyk *et al.* 2015). The long-term outcome of the disease is also affected by the number of relapses and the quality of remission achieved (Emsley *et al.* 2013).

It is assumed that there are specific pathophysiological processes underlying various symptoms of SCZ and it has been found that several neurotransmission pathways are dysfunctional (Howes & Nour, 2016). Different hypotheses have been suggested to explain the origin of SCZ, including the genetic hypothesis (Mowry & Nancarrow, 2001; Ripke *et al.* 2014), dopamine hypothesis (Snyder, 1976; Carlsson, 1988; Davis *et al*. 1991), glutamate hypothesis (Kim *et al*. 1980), neurodevelopment hypothesis (Weinberger, 1987; Murray & Lewis, 1987), inflammation hypothesis (Maes *et al.* 1995; Naudin *et al.* 1996; Lin *et al.* 1998; Fan *et al.* 2007; Miller *et al.* 2011; Kirkpatrick & Miller 2013), OxS hypothesis (Reddy & Yao 1996; Mahadik *et al.* 2003; Do *et al.* 2009; Zhang *et al.* 2010), and mitochondrial dysfunction hypothesis (Ben-Shachar 2002). Each of these hypotheses approaches the pathophysiology of SCZ from a different point of view with evidence from clinical and experimental studies. However, a complete understanding of the disease mechanism remains elusive, as not only the pathophysiological aspects and treatment effects vary between different phases of the disease, but also qualitative and quantitative differences in biomarker levels have been described. The focus in this thesis is limited to the early stage of chronic psychotic disorder, i.e. FEP.

2.2. First-episode psychosis and different biomarkers

Biomarkers related to pathological conditions are crucial regarding both their scientific and clinical impact. There are several definitions of biomarkers described by Ptolemy and Rifai (2010): National Institutes of Health define a biomarker as *"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"*; the International Program on Chemical Safety define a biomarker as *"any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease"* and WHO states *"almost any measurement*

reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological can be defined as a biomarker and the measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction" (http://www.inchem.org/documents/ehc/ehc/ehc155.htm, International Programme on Chemical Safety – IPCS). Despite all such detailed definitions, biomarkers can be divided into common/routine and more specific/indicative. It is obvious that studies targeted to find out more indicative possible biomarkers have the potential to translate from "bench to bedside".

Regarding psychosis, including FEP, one important and growing area of contemporary research is focused on identification of circulating lipidomics-, inflammation- and OxS-related indicative biomarkers, including novel ones. In summary, such information gathered from patients with FEP before and after antipsychotic treatment and compared to the information gathered from control subjects (CS) may elucidate some new aspects considering both the pathogenesis of FEP and treatment effects (positive and negative) in order to work out better clinical strategies in the future.

2.2.1. First-episode psychosis and lipidomics

Lipidomic studies are conducted to help determine the biochemical mechanisms of lipid-related disease processes by detecting changes in cellular lipid metabolism, trafficking and homeostasis. In this thesis, the focus on lipidomics is specifically targeted to acylcarnitines (ACs), since there are very limited data available on the ACs profile in FEP patients. It is known that SCZ is associated with elevated fasting total triglycerides and insulin resistance (Suvisaari *et al.* 2007), but this metabolic abnormality has generally been attributed to specific side effects of antipsychotic drugs (Meyer *et al.* 2008). Studies on treatment-naïve FEP patients have already detected impaired glucose tolerance, and elevated insulin and metabolic abnormalities (van Nimwegen *et al.* 2008; Fernandez-Egea *et al.* 2009; Steiner *et al.* 2010; Guest *et al.* 2010; Guest *et al.* 2011; Kirkpatrick *et al.* 2012) which are not caused by poor health habits (Kirkpatrick *et al.* 2012).

ACs (from short-chain to long-chain, from C2 to C18) are the intermediates of the fatty acid β-oxidation process and are formed, using carnitine (CARN), to maintain the balance between free and esterified coenzyme-A (CoA), which is relevant for normal cell function. ACs are produced via transfer of the acyl group of a fatty acyl-CoA to L-carnitine by carnitine transferases. L-carnitine is relevant for transporting activated long-chain fatty acids from cytosol into mitochondria where oxidation of fatty acids occurs. After transport through the mitochondrial membrane, the acyl-CoA is converted to ACs by carnitine palmitoyltransferase 1 (CPT-1) (Coleman *et al.* 2002). CPT-1 is one of the most important regulators of long-chain fatty acid oxidation (McGarry *et al*. 1977). In the mitochondrial matrix, CPT-2 re-converts ACs back into free CARN and

long-chain acyl-CoA that can proceed to oxidation (Ramsay *et al*. 2001). The ACs which are transported through the cell membrane circulate in plasma. The physiological role of the ACs efflux to plasma is not completely known, but the formation of ACs prevents CoA from being trapped and therefore enables continuation of CoA dependent metabolic processes (Lopaschuk *et al.* 1994).

Biochemical analysis of serum/plasma ACs helps detect inheritable disorders of fatty acid oxidation (FAO) enzymes. The latter tend to accumulate due to metabolic dysfunction of β-oxidation and tricarboxylic acid cycle in mitochondria (Mihalik *et al.* 2010). Plasma ACs levels generally vary due to increases in long-chain ACs (LCACs) levels, which are usually a result of problematic FAO (Mihalik *et al*. 2010; Muoio & Koves 2007). In addition to using LCACs as biomarkers, a variety of studies support the hypothesis that LCACs can activate pro-inflammatory signalling pathways (Kouttab & Simone, 1993; Rutkowsky *et al*. 2014; McCoin *et al.* 2015a, b) and have implications for insulin resistance (Mihalik *et al.* 2010; Schooneman *et al*. 2013). Muoio and colleagues (Muoio & Koves 2007; Koves *et al.* 2008; Muoio & Neufer 2012) proposed an alternative mechanism in which FAO rate exceeds the tricarboxylic acid cycle (TCA), leading to the accumulation of intermediate metabolites such as ACs, which can interfere with insulin sensitivity.

The concept of lipotoxicity is usually associated with the obesity-induced impairment of insulin sensitivity, and increasingly more attention is paid to intra-mitochondrial changes and impairments in FAO, thereby focusing on ACs (Muoio & Koves, 2007). Evidence shows that ACs have distinct functions in mitochondrial lipid metabolism. The trans-membrane export of ACs suggests that they not only prevent the accumulation of noxious acyl-CoAs but also release CoA from being trapped, which is relevant for the regulation of many metabolic pathways (Lopaschuk *et al.* 1994; Ramsay *et al.* 2001). In addition, the metabolism of short-chain ACs (SCACs) and the interaction of acetyl-CoA and ACs via carnitine acetyl-CoA transferase (CrAT) may regulate the pyruvate dehydrogenase complex and thus influence glucose oxidation (Muoio *et al.* 2012). Besides for mitochondria the need to release CoA and export acetyl-CoA, ACs may simply reflect the FAO flux.

In previous studies, special attention is paid to the shortest AC, acetylcarnitine, due to the controlling role of acetyl-CoA on substrate switching and thus metabolic flexibility. The mitochondrial enzyme CrAT converts acetyl-CoA to membrane permeable acetylcarnitine and allows mitochondrial outflow of excess acetyl-CoA that otherwise could inhibit pyruvate dehydrogenase (Muoio *et al.* 2012). In contrast to lower CrAT expression in diabetic subjects, plasma ACs levels showed significant positive correlation with glycated hemoglobin (HbA1c) levels over a wide range of insulin sensitivity, indicating an increase in CrAT activity in insulin-resistant states (Adams *et al.* 2009).

Metabolomic studies have found the evidence that branched-chain and aromatic amino acids (isoleucine, leucine, valine, tyrosine, and phenylalanine) (Fiehn *et al.* 2010) are significantly correlated with present or future diabetes (Newgard *et al.* 2009; Fiehn *et al.* 2010; Wang *et al.* 2011). In accordance with

the latter, branched-chain amino acid-derived C3- and C5-carnitine, together with FA-derived C6- and C8-carnitine, tend to be higher in obese and type 2 diabetes mellitus subjects compared with lean controls (Mihalik *et al.* 2010; Newgard *et al.* 2009). In the same study, C4-dicarboxylcarnitine (C4DC-carnitine), which is also formed during branched-chain amino acid metabolism, indicated positive correlation with basal glucose levels and HbA1c (Mihalik *et al.* 2010).

Long-chain FAs (such as palmitic acids) are linked to insulin resistance and making the role for LCACs such as C16 in insulin resistance supposable (Holland *et al.* 2007; Samuel & Shulman 2012). In comparison with lean controls, obese and insulin-resistant people had higher plasma LCACs levels (Mihalik *et al.* 2010) and after insulin infusion, there was a decrease in overall LCACs, but to a lesser extent in diabetic patients. This is consistent with lower resting energy expenditure and indicates ongoing FAO or lipid flux (metabolic inflexibility) (Mihalik *et al.* 2010). Moderate correlations between ACs profiles and different clinical characteristics (i.e., higher body mass index (BMI), basal free FA levels, insulin sensitivity) indicate a causal relationship. The more insulin-sensitive the subjects are, the more capable they are at metabolizing FAs. Thus, ACs with longer chain lengths are associated with insulin resistance, which seems to coincide with the known effects of long-chain FAs on insulin signalling. ACs can also be found in cell membranes due to their amphipathic nature. Longer chain length promotes merging into the membrane phase (e.g., C16- and 18-carnitine) (Ho *et al.* 2002). By contrast, ACs appear to be tracked with higher lipid flux and as such may only refer to higher FAO.

The whole set of ACs has not been studied in FEP patients' population before, however, studies on SCZ and FEP have shown that psychotic disorders change the composition of brain lipids and lipid homeostasis, which may be affected by antipsychotics as well (Kaddurah-Daouk & Krishnan *et al*. 2009; Polymeropoulos *et al*. 2009; McEvoy *et al*. 2013). The alterations in the whole ACs profile in FEP remain to be elucidated; however, as their metabolism is interrelated to a variety of other processes (e.g. glycose oxidation, insulin sensitivity, metabolic syndrome and pro-inflammatory changes.), it may provide relevant insight to the pathogenesis of FEP.

2.2.2. First-episode psychosis and inflammation

The profile of inflammatory biomarkers can be related to the clinical status of the FEP patient (Miller *et al.* 2011; Kirkpatrick & Miller 2013) and change in this profile may be related to the therapeutic effect of antipsychotic treatment (Kirkpatrick & Miller 2013; Fond *et al.* 2015; Lai *et al.* 2016). Numerous studies have found that there is an imbalance of inflammatory biomarkers in the chronic phase of SCZ (Kirkpatrick & Miller 2013) as well as in FEP (Miller *et al.* 2011; Fond *et al.* 2015). Studies on treatment-naïve FEP patients show an increase in peripheral pro-inflammatory biomarkers and, at the same time, these

results are not influenced by the effects of antipsychotic treatment (Miller *et al.* 2011; Kirkpatrick & Miller 2013; Fond *et al.* 2015). However, no final consensus has been achieved over which pro- and anti-inflammatory proteomics biomarkers or their combinations are involved in the signature of FEP.

Cytokines (CKs) include a large number of predominantly pro-inflammatory proteins, such as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors (TGFs), and chemokines, which are involved in the regulation of immunologic and inflammatory responses in physiologic and pathologic conditions (Steinke & Borish 2006). It has also been found that CKs regulate dopaminergic and serotoninergic neurotransmission (Felger & Miller 2012; Baganz & Blakely 2013). These molecules are synthesized and secreted by various types of cells, including not only immune cells, such as T-lymphocytes, natural killer (NK) cells, monocytes/macrophages, polymorphonuclear leukocytes, dendritic cells, and microglia, but also non-immune cells, such as adipocytes, neurons, fibroblasts, and endothelial cells. CKs coordinate the responses of cells of the innate immune system (monocyte/macrophages, polymorphonuclear leukocytes, and NK cells) and those of the adaptive immune system (e.g., T- and B-lymphocytes). Changes in the levels of some CKs seem to be the main culprit of the immune and inflammatory abnormalities documented in SCZ and FEP (Leonard *et al.* 2012), and even minimal changes in CK levels could possibly lead to functional impairments (Altamura *et al.* 2013).

The **IL-1β, IL-2, IL-6, IL-8, IFN-γ, TNF-α** are considered **pro-inflammatory CKs**, in the sense that they enhance the immune response and are essential to the inflammatory response by contributing to febrile response, activating phagocytotic cells such as macrophages, facilitating vascular permeability, and promoting the release of plasma-derived inflammatory mediators such as bradykinin and components of the complement system (Curfs *et al.* 1997; Gallin *et al.* 1999). The **IL-10,** also **IL-4,** IL-1 receptor antagonist (IL-1RA), and soluble IL-2 receptor (sIL_2R) are **anti-inflammatory** CKs that down-regulate inflammation via immunosuppressive functions (Potvin *et al.* 2008, Fonseka *et al.* 2016). Thus, the following brief overview focuses on the above-mentioned more prominent biomarkers.

IL-6 is a pro-inflammatory CK that plays a central role in the inflammatory process (Chase *et al.* 2016; Mitra *et al.* 2017). The main sources of this CK are monocytes and macrophages at the site of injury during acute inflammation, as well as T-cells in chronic inflammation. In homeostatic conditions, the levels of IL-6 are low, but IL-6 serum levels increase rapidly with stress. Numerous studies have shown that IL-6 modulates various aspects of the innate immune system, such as hematopoiesis and influx of neutrophils at sites of infection or trauma (Liu *et al.* 1997; Chou *et al.* 2012). In addition, this CK induces the synthesis of C-reactive protein (CRP), serum amyloid A, and fibrinogen, as acute phase proteins (Borovcanin *et al.* 2017). **IL-1β** is released primarily by monocytes and macrophages, as well as by non-immune cells, such as fibroblasts and endothelial cells, during infection, inflammation, cell damage, and invasion (Zhang & An,

2007). **TNF-α and IL-1** are the inducers of endothelial adhesion molecules, which are essential for the adhesion of leukocytes to the endothelial surface prior to migration into the tissues. IL-1 is the inductor of gene expression for type II phospholipase A2 (PLA2) and cyclooxygenase 2 (COX-2). IL-1 induces the transcription of COX-2 and has apparently little effect on increasing cyclo-oxygenase 1 (COX-1) production (Dinarello 2000). TNF-α is a multifunctional pro-inflammatory CK, with effects on lipid metabolism, insulin resistance, endothelial function, and coagulation. TNF-α, a pro-inflammatory CK, is produced by many types of cells, including lymphocytes, macrophages, fibroblasts and keratinocytes, in response to infection, inflammation, and other types of environmental stress. **IL-8** is a prototypical chemokine and the neutrophil chemoattractant, which also activates neutrophils for degranulation and causes tissue damage (Dinarello 2000). Biologically active **IFN-γ** is produced by mitogen activated T-lymphocytes and natural killer cells and its primary function is involvement in the regulation of immunological functions that are essential in protecting the host against viral and some bacterial and protozoal infections (Schoenborn & Wilson 2007). IFN-γ is an important activator of macrophages and induces the expression of Class II major histocompatibility complex (MHC) molecule. Aberrant expression of IFN-γ is associated with several auto-inflammatory and autoimmune diseases. The importance of IFN-γ in the immune system partly derives from its ability to inhibit viral replication directly and, most importantly, from its immunostimulatory and immunomodulatory effects.

CKs, such as IL-4, IL-10, IL-13, and transforming growth factor beta (TGF-β) inhibit the production of IL-1, TNF-α, chemokines such as IL-8, and vascular adhesion molecules (Dinarello 2000). **IL-10** is a CK with highly potent anti-inflammatory properties (Murray 2006) and able to inhibit the expression of other inflammatory CKs such as TNF-α, IL-6 and IL-1 by activated macrophages. In addition, IL-10 can up-regulate endogenous anti-cytokines and down-regulate pro-inflammatory cytokine receptors. Thus, it can counter-regulate the production and function of pro-inflammatory cytokines at multiple levels (Zhang & An 2007). Therefore, loss of IL-10 function can cause excessive and often damaging inflammation (Murray 2006). **IL-4** regulates humoral and adaptive immunity, stimulates B-cells and T-cells and influences the differentiation of B-cells into plasma cells, and is a key CK in the initiation of a type-2 inflammatory response, i.e. production of immunoglobulin E (IgE) antibodies (Borovcanin *et al.* 2013). IL-4 is a CK with potent anti-inflammatory properties, supressing the expression of inflammatory CKs such as TNF-α, IL-6 and IL-1 by activated macrophages.

Among other inflammatory biomarkers, the role of ferritin, CRP and plasminogen activator inhibitor-1 (PAI-1) in FEP remains to be evaluated. **Ferritin** is an iron-binding molecule that stores iron in a bioavailable form and is widely acknowledged as a non-specific acute-phase reactant and inflammatory marker (Sharif *et al.* 2018). Serum ferritin is also a well-known inflammatory marker, and abnormally high serum ferritin levels are a consequence of cell stress and

damage (Kell & Pretorius 2014). It has been proved that inflammation and OxS increase the synthesis of ferritin in multiple cells, including macrophages (Sharif *et al.* 2018). **CRP** is an acute-phase protein of hepatic origin, which increases after IL-6 secretion by macrophages and T-cells. It is a trustworthy marker of subclinical and systemic inflammatory conditions (Windgassen *et al.* 2011) and a common final denominator in the inflammation cascade (Lopresti *et al.* 2014). It has also been associated with metabolic dysregulation, since it is synthesized by the liver in response to factors released by macrophages (Pepys & Hirschfield, 2003) and fat cells (adipocytes) (Lau *et al.* 2005) and is widely observed in patients with SCZ (Vuksan-Cusa *et al.* 2010; Vuksan-Cusa *et al.* 2013). **PAI-1**, also known as an endothelial plasminogen activator inhibitor, is a protein that at elevated levels is a risk factor for thrombosis and atherosclerosis as it inhibits fibrinolysis. PAI-1 is produced mainly by the endothelium, but it can also be secreted by adipose tissue or other tissues. The level of PAI-1 is increased in metabolic syndrome but also in inflammatory conditions where fibrin is deposited in tissues, as it appears to favour the progression of fibrosis. (Vaughan 2005)

Various studies on medication-naïve FEP patients have described the up-regulation of peripheral IL-1β, IL-6, and TNF-α levels (Akiyama 1999; van Kammen *et al.* 1999; Theodoropoulou *et al.* 2001; Sirota *et al.* 2005; Na & Kim 2007; Kim *et al.* 2009; Song *et al.* 2009), but later meta-analyses report the elevation of IL-1β, IL-6, IL-12, IFN-γ, TNF-α, TGF-β, interleukin 2 receptor (IL-2R), soluble IL-2R levels, and IL-17 (Fond *et al.* 2015; Fraguas *et al.* 2017). Although the elevation of TNF-α (Fond *et al.* 2015, Fraguas *et al.* 2017) and IL-6 has been the most repeated finding in FEP, lack of consistency in the results of CKs have been noted by many authors (Kronfol & Remick 2000; Muller *et al.* 1999; Gladkevich *et al.* 2004). Decreased levels of IL-1β and IFN-γ, and increased levels of IL-12 and sIL-2R have been reported after antipsychotic administration (Tourjman *et al.* 2013; Crespo-Facorro *et al.* 2012; MacDowell *et al.* 2013). Decreased IL-6 levels, elevated levels of IL-10, and normalization of T helper 17 cells were all associated with positive treatment response (Upthegrove *et al.* 2014; Kubistova *et al.* 2012; de Witte *et al.* 2014; Ding *et al.* 2014).

Considering the above-mentioned inflammation-related markers, our group also established that FEP patients have significantly higher levels of IL-4 and IL-6 and significantly reduced levels of IL-1β before the start of antipsychotic treatment, in comparison with control subjects (Haring *et al*. 2015). The circulating levels of IL-2, IL-6, IFN-γ, IL-4, IL-8 and IL-1α were significantly lower in treated FEP patients compared to medication-naïve subjects (Haring *et al*. 2015). Antipsychotic treatment resulted in a significant clinical improvement of FEP and suppression of positive symptoms was in correlation with decreased levels of IL-2 and IL-4 but was accompanied with a significant increase in the BMI (Haring *et al*. 2015).

The most plausible conclusion is that there is a chronic, low-grade inflammatory change related to FEP and that effective treatment significantly alleviates these changes. However, there still exist some inconsistencies regarding the selection of inflammatory biomarkers specific for FEP.

2.2.3. First-episode psychosis and oxidative stress

Several studies support the understanding that both susceptibility to OxS and the status (level) of OxS may underlie the pathogenesis of SCZ via some mechanisms (Ng *et al.* 2008). Deterioration in schizophrenic illness is partly contributed by OxS (Mahadik & Scheffer 1996; Mahadik *et al.* 2001; Michel *et al.* 2004; Yegin *et al.* 2012). OxS refers to an abnormal increase in free radicals and reactive oxygen species (ROS), highly reactive molecules that are generated from metabolism – including neurotransmitters associated with SCZ such as dopamine and glutamate – and environmental exposures that increase an imbalance in the pro-oxidant/antioxidant levels, leading to potential cell damage (Flatow *et al.* 2013). Free radicals are unstable atoms or molecules containing an odd (unpaired) electron(s) in the outer orbit, which can initiate a toxic chain reaction in the cell membrane or important cellular components, including DNA (Patel *et al.* 2017). The most common free radicals in a biological system are radical derivatives of oxygen (ROS) and nitrogen (reactive nitrogen species – RNS, "nitrosative stress").

The most important ROS in humans are hydrogen peroxide (H_2O_2), superoxide radical (O_2•−), and hydroxyl radical (OH•). Mitochondria, but also endoplasmic reticulum and peroxisomes, are notable contributors in generating ROS (Patel *et al.* 2017). RNS include nitric oxide (NO) and peroxinitrite (ONOO•) (Bitanihirwe & Woo 2011). Other biologically important free radicals include lipid hydroperoxide (ROOH), lipid peroxyl radical (ROO•), and lipid alkoxyl radical (RO•), which are associated with membrane lipids. Thiol radical has an unpaired electron on the sulfur atom that is responsible for the formation of the deoxyribonucleic acids, but thiyl intermediates are also produced by the oxidation of glutathione (GSH) (Kurutas 2016).

Decreased levels of antioxidants and increased production of reactive species (RS) will ultimately lead to oxidative damage to macromolecules such as proteins and lipids, nucleic acids, as well as changes in modulation of the intracellular signalling pathway, gene expression and deleterious changes in the activity of critical cellular enzymes (e.g. caspases), which can lead to cell death (Halliwell 2006a; Cai *et al.* 1998; Evans *et al.* 2004; Scherz-Shouval & Elazar 2007; Pawełczyk *et al.* 2017). Lipid peroxidation is a well-characterized effect of ROS that causes damage to the cell membrane, as well as to the membranes of cellular organelles, such as mitochondria (Pawełczyk *et al.* 2017).

Fortunately, there are several cellular antioxidant defence mechanisms to counterbalance the production of ROS and RNS, including enzymatic and non-enzymatic pathways (Nordberg & Arner 2001). Biological systems have developed complex protection strategies against free radical toxicity. Under physiological conditions, the potential for free radical damage is kept under control by the antioxidant defence system (AODS) containing a series of enzymatic and non-enzymatic components that act cooperatively at different sites in the free radical pathways. A dynamic state is kept in check during the redox coupling under normal conditions (Yao *et al.* 2006).

Antioxidant enzymes that constitute the important defence system in our body against OxS include catalase (CAT), glutathione peroxidase (Gpx) and super oxide dismutase (SOD) that block the chain reaction of RS (Halliwell, 2006a, b). In purine catabolism, xanthine oxidase catalyzes the conversion of xanthine to uric acid, which is an important antioxidant, and also generates superoxide radicals that are catalysed by SOD to hydrogen peroxide (Flatow *et al.* 2013). Both CAT and Gpx participate in the conversion of hydrogen peroxide to water and oxygen, but Gpx is also able to eliminate an excess of ROOH. GSH is a crucial non-enzymatic antioxidant in the cells. During elimination of RS, GSH is converted to oxidized glutathione (GSSG) by Gpx. Gpx also converts nitrate (a by-product of NO radicals) to nitrite that is often used as a marker for NO activity (Flatow *et al.* 2013). Hydroxyl radicals, produced from both hydrogen peroxide and NO, contribute to lipid peroxidation, protein carbonylation, DNA damage, and apoptosis. Vitamin E (α-tocopherol), acting as an antioxidant, can inhibit lipid peroxidation. In turn, the resulting vitamin E radicals can be recycled by vitamin C. Thiobarbituric acid reactive substances (TBARS), being important end products of lipid peroxidation, measure endogenous malondialdehyde (MDA) (Flatow *et al.* 2013).

The status of OxS signature involves the levels of several biomarkers such as total anti-oxidative status, OxS index, lipid peroxidation and protein-related (e.g. the ratio of methionine sulfoxide to methionine) biomarkers. Therefore, to establish the status of OxS, several biomarkers should be measured simultaneously.

Data on the status of OxS in SCZ and FEP are controversial. Several studies have documented alterations in antioxidant enzymes in SCZ, but this is not always consistent. While reduced levels of the antioxidant enzymes are generally reported in patients with SCZ compared to controls (Dadheech *et al.* 2008; Singh *et al.* 2008; Raffa *et al.* 2009), other studies have reported either no change (Srivastava *et al.* 2001) or an improvement in antioxidant status in SCZ (Kuloglu *et al.* 2002; Dakhale *et al.* 2004; Kunz *et al.* 2008). Zhang *et al.* (2010) reported findings of increased NO and TBARS in patients with SCZ. Both of these are involved in the oxidative degradation of lipids, affect polyunsaturated fatty acids, and thereby damage the cell membranes, implicating lipid messenger signalling and DNA structure. In the same meta-analyses, the same authors reported the activities of SOD to be significantly decreased in disorganized SCZ patients, which supports the theory that the alteration of the OxS and mitochondrial function might underlie the pathophysiology of SCZ (Zhang *et al.* 2010). Flatow *et al.* 2013 explored OxS markers in patients with early stage of SCZ and reported reduced levels of antioxidants – total antioxidant status (TAS) as well as plasma nitrite and uric acid, plasma nitrites, red blood cell (RBC) catalase, and SOD in RBC – in patients with FEP, but on the other hand, significantly increased levels of plasma TBARS, MDA, and SOD in FEP patients versus CS. The levels of TBARS coincide with the findings by Zhang *et al.* (2010), except for the levels of plasma SOD. Recently it was shown that changes in some OxS markers (lipid or protein oxidation or nitric oxide

production) were insignificant in FEP patients compared to CS (Noto *et al*. 2015). The major findings of the meta-analysis performed by Noto *et al.* (2015) revealed that FEP is accompanied by decreased paraoxonase 1 (PON1) and increased total radical-trapping antioxidant parameter (TRAP) levels as compared to CS, and that treatment with risperidone increases PON1 and decreases ROOH levels. TRAP levels are determined by the effects of some specific non-enzymatic antioxidants in the plasma, including uric acid, albumin, bilirubin, protein-bound thiol groups, and vitamins E and C (Halliwell, 1996). Thus, in theory, the elevation in TRAP in FEP patients may indicate an increase in any of these analyses that determine TRAP. It is possible that the increase in TRAP is an early compensatory process, which may counterbalance the increase in ROS production. These results are not in line with those of a previous meta-analysis showing that lipid peroxidation (as measured with TBARS) and NO are increased in SCZ (Zhang *et al.* 2010).

As seen from the results of different meta-analyses, the information regarding OxS parameter changes in FEP is inconsistent and in some cases contradictory and this issue still lacks clarity. Therefore, further studies are needed to collect repetitive data and gain a thorough understanding of how the OxS status may be related to different phases of SCZ.

2.3. Summary of literature

Lipidomics, inflammation and OxS are exquisitely related processes. Chronic low-grade inflammation is associated with elevated levels of ROS that initiate lipid peroxidation. And conversely, elevated OxS triggers inflammation, whereas redox balance inhibits the cellular response. Therefore, OxS and inflammation may be seen as both causes and consequences of cellular pathology in a number of disorders including FEP (Terlecky *et al.* 2012). As the results of the studies reveal, some aspects of lipidomics, inflammation and OxS have been investigated in relation to psychosis, but there are still unanswered questions or contradictory data concerning the status of FEP patients. Therefore, the current thesis was aimed to obtain information on lipidomics (ACs), inflammation and OxS status in FEP patients compared to a carefully selected control group, and to compare the metabolomic status of FEP patients before and after seven-month antipsychotic treatment.

3. AIMS OF THE THESIS

The general aim of the study was to profile the serum levels of ACs (lipidomics), inflammatory and OxS biomarkers in FEP patients before and after antipsychotic treatment and to analyse relationships and interplay between inflammation and OxS status and alterations in ACs in FEP patients.

Specific aims:

1. To determine the signature of ACs in patients with FEP before and after seven-month antipsychotic treatment,
2. To examine the inflammatory signature in patients with FEP before and after seven-month antipsychotic treatment,
3. To examine the OxS status in patients with FEP before and after seven-month antipsychotic treatment,
4. To summarize the bioinformation on the changes of assayed biomarkers in patients with FEP before and after seven-month antipsychotic treatment.

4. SUBJECTS AND METHODS

4.1. Subjects

4.1.1. First-episode psychosis patients

Patients were recruited from the Psychiatry Clinic of Tartu University Hospital, Estonia, and 38 FEP patients (21 male and 17 female; mean age 25.4 ± 0.89 years) gave their consent to participate in the study. In order to be enrolled, the patients needed to meet the following inclusion criteria: age between 18 and 45 years; experienced FEP; duration of untreated psychosis less than 3 years; being antipsychotic-naïve until the first contact with medical services for psychosis.

Patients were not included in the study, if they met the following exclusion criteria: psychotic disorders due to a general medical condition or substance induced psychosis. FEP was diagnosed based on clinical interviews according to the International Classification of Diseases, Tenth Edition (ICD-10) (World Health Organization 1992) criteria.

4.1.2. First-episode psychosis patients and their treatment

Thirty-six FEP patients out of 38 were allocated to antipsychotic treatment (two refused) and were included in follow-up analysis. Information on antipsychotic medication use was collected from patients' medical records. The patients were treated according to standard of care with different antipsychotics based on the clinical need. During the follow-up period, the patients received either atypical (n=24), typical (n=1) or mixed (n=11) antipsychotic medication; the mean theoretical chlorpromazine dose equivalent (Gardner *et al.* 2010) was 396 ± 154 (range 80–640) mg. Twenty-seven patients were treated with only antipsychotics, 4 patients additionally needed mood stabilizers and 6 patients also received antidepressants or hypnotics. During the second blood collection, 13 patients received quetiapine (including 7 cases as only antipsychotic treatment), 10 patients received aripiprazole (3 cases as only antipsychotic treatment), 12 were treated with olanzapine (9 cases as only antipsychotic treatment), 2 patients were assigned to risperidone (1 case as only treatment), 2 patients to sertindole (1 case as only antipsychotic treatment), 3 patients to ziprasidone, 2 patients to clozapine (in both cases clozapine was administered in combination with other psychotropic drugs) and 2 patients to perfenazine (1 case as only treatment).

4.1.3. Control subjects

The sample of CS was recruited by advertising in the same geographical area as the FEP patients and altogether 37 mentally healthy subjects (16 male and 21 female, mean age 24.8 ± 0.86 years) were recruited. The CS were interviewed by experienced psychiatrists in order to exclude people with mental disorders. The exclusion criteria for the control group also included psychotic disorders among close relatives. Participants were enrolled between September 2009 and December 2013. To retain the naturalistic study design, the study participants were not excluded due to cigarette smoking and/or substance abuse. Eight patients (21.1%, all men) and 7 CS (18.9%, three of which were men) were active cigarette smokers. In addition, 10 patients (8 of whom were the same who were current cigarette smokers), and one CS (also a cigarette smoker) had used cannabis during his/her lifetime.

All participants were monitored for symptoms of infections or severe systemic somatic illness throughout the study period. None of the study participants dropped out for that reason.

4.2. Study design and protocol

This study consisted of two phases: the enrolment phase (on admission to hospital) and the follow-up phase (mean duration 7.18 ± 0.73 months). For the FEP patients, fasting blood samples, clinical, demographic and BMI data were collected at these 2 time-points. The period between enrolment and the follow-up phase consisted of an initial stabilization of acute psychotic symptoms (approximate duration of a month) and a further continuous six-month antipsychotic treatment. Symptom severity was measured using Positive and Negative Syndrome Scale (PANSS) (Kay *et al*. 1987), a rating instrument that evaluates the presence and severity of positive and negative symptoms and general psychopathology. PANSS consists of thirty items, scored from 1 (absent) to 7 (severe) for the assessment and clinical monitoring of the course of disease and response to antipsychotic treatment. Physical examination included the evaluation of BMI [weight (kg)/ height (m)2] data. Blood samples, BMI, and demographic data were also collected from the CS. The study was approved by the Research Ethics Committee of the University of Tartu, Estonia (initial approval No 177/T-2 issued on 15Feb2008 and follow-up approval No 211/M-22 issued on 23Jan2012). Written informed consent was obtained from all study participants.

4.2.1. Blood collection and clinical laboratory measurements

Fasting blood samples (5 mL) from the study participants were collected into anticoagulant-free tubes using the standard venipuncture technique between 9 a.m. and 11 a.m. The samples were kept for 1 hour at 4 ^{o}C (for platelet activation) before centrifugation at 2,000 rpm for 15 minutes at 4 ^{o}C and removal of serum. The serum was kept at –20 ^{o}C before testing.

4.2.2. Measurement of biomarkers

4.2.2.1. Measurement of acylcarnitines, methionine and methionine sulfoxide

The serum levels of ACs, oxidized methionine (methionine sulfoxide, Met-SO) and methionine (Met) were measured with the AbsoluteIDQ™ p180 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria) that enables detection of 188 endogenous metabolites and 45 metabolite ratios via a combination of flow injection analysis and the liquid chromatograph tandem mass spectrometry technique. The Biocrates AbsoluteIDQ p180 kit is a commercially available targeted metabolomics assay and it is used in many studies of human serum and plasma, including clinical studies. The measurements were made according to the manufacturer's manual UM-P180. Identification and quantification of the metabolites were achieved via monitoring multiple reactions along with internal standards. Of all statistically important changes of ACs, only these values were used that were at least 2.3 times higher than the level of detection (LOD) given in the manual of the Biocrates AbsoluteIDQ p180. The metabolite concentrations were calculated linearly using a combination of Analyst (ABSciex, Framingham, USA) software and MetIDQ (Biocrates Life Sciences AG, Innsbruck, Austria) software. To ensure the quality of data, the values were checked based on the LOD. The absolute minimum LOD for a metabolite is largely dependent on the sensitivity of the mass-spectrometer and ionization of the metabolite.

4.2.2.2. Measurement of inflammatory biomarkers

Biochip array technology (Randox Biochip, RANDOX Laboratories Ltd, Crumlin, U.K., Metabolic Syndrome Array I for Evidence Investigator^{TM}) was used to perform simultaneous quantitative detection of multiple analytes from a single serum sample of FEP patients or CS for inflammatory biomarkers that were measured according to the manufacturer's protocol: TNF-α, IL-1α, IL-6, ferritin and PAI-1. Assay sensitivity varied from picograms to nanograms per millilitre. The reproducibility of the assay for an individual CK was determined using the quality controls provided with the kit (Kaur *et al*. 2012, Di Nicola *et al*. 2013).

4.2.2.3. Measurement of oxidative stress markers

Measurement of total peroxide (TPX) concentration is based on the oxidation of ferrous ion to ferric ion by various types of peroxides. The samples were analysed using the OXYSTAT Assay Kit Cat. No BI-5007 (Biomedica Gruppe, Biomedica Medizinprodukte GmbH & Co Kg, Wien). Peroxide concentrations are detected based on the reaction of biological peroxides with peroxidase and the formation of a coloured ferric-xylenol orange complex. The absorbance of the latter can be measured photometrically at 450 nm, using the ELISA plate reader Photometer Sunrise (Tecan Austria GmbH, Salzburg). For the assay, a calibrator calculates the concentration of biological peroxides in the sample. Results show direct correlation between free radicals and circulating biological peroxides, thus allowing characterization of the oxidative status in biological samples. The concentration is stated as H_2O_2-equivalents (µmol/L).

A new more stable coloured 2,2`-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical ($ABTS^{*+}$) was used for the measurement of total antioxidative capacity (TAC). The basic principle of the method is that a colourless molecule, reduced ABTS, is oxidized to a characteristic blue-green $ABTS^{*+}$, using hydrogen peroxide in acidic solution (the acetate buffer 30 mmol/L pH 3.6). When the coloured $ABTS^{*+}$ is mixed with any reducing substance, colourless ABTS is formed again. The $ABTS^{*+}$ is decolorized by antioxidants according to their concentrations and antioxidant capacities and bleaching rate is inversely related to the TAC of the sample. This change in colour is measured as a difference in absorbance at 660 nm. The reaction rate is calibrated with Trolox, which is used as a traditional standard for TAC measurement assays and the results are expressed in mmol Trolox equivalent/L. The within- and between-batch precision data obtained by TAC method were 2.5% and 2.9%, respectively. The ratio of TPX to TAC in percentage is used as OxS index (OSI), an indicator of the degree of OxS (Kaldur *et al.* 2014). Thus, OSI was calculated according to the following formula: OSI = [(TPX, µmol/L): (TAC, µmol/L) x 100)].

4.2.3. Statistical analyses

Between-group differences in the demographic data were analysed using the *t*-test for continuous variables and chi-square test for categorical variables. The Shapiro-Wilk test was applied to test for normality assumption. Therefore, non-parametric statistical methods were used to establish between- and within-group differences in biomarker levels. The Mann-Whitney *U*-test was applied to compare the raw data of two independent samples (FEP patients' pre-treatment condition versus CS). Wilcoxon signed rank test was used for analysing OxS markers and Wilcoxon matched pairs test was used for ACs and inflammatory markers to compare two dependent samples (FEP patients before and after treatment). For within-subjects' analyses, the patients were paired one by one. The Bonferroni correction was applied for the number of biomarkers within

Mann-Whitney *U*-test and Wilcoxon signed rank test (Miller, 1981) in order to diminish the likelihood of type I error. Differences between the FEP patients and CS (based on the Mann-Whitney *U*-test), and differences between the pre- and post-treatment values within the patient group (based on the Wilcoxon matched pairs test), regarding serum ACs levels, were considered statistically significant at $p < 0.05$ throughout the analyses. To demonstrate effect size (eta^2) estimates for the non-parametric tests, the values of squared standardized test statistics (*Z*) were divided by the total number of observations on which Z was based. Effect sizes were interpreted as small, medium, and large, with the corresponding eta-squared ranging from 0.01–0.05, 0.06–0.13, and ≥0.14, respectively (Cohen, 1988).

To find the correlations between OxS, low-grade inflammation and metabolic markers in FEP patients' group before and after 7-month antipsychotic treatment, Spearman's rank correlation analysis was applied.

In order to demonstrate between-group differences for biomarkers levels (i.e. drug-naïve FEP patient versus CS, and FEP patients after treatment versus CS) and within-group changes (i.e. drug-naïve FEP patients versus FEP patients after treatment), general linear models (GLM) were applied. The biomarker values were $\log_{10}$-transformed to approximate normality as GLM analyses required normally distributed data. Categorical (disease, gender, smoking status) and continuous (age) covariates were used in the GLM to compare biomarker and OxS levels (dependent variables) between the groups. An independent variable was used to study within-subjects' differences in pre- and post-treatment OxS conditions. In the next step, backward variable elimination was used until the best model fit was reached. Each subsequent step removed the least significant variable in the model until all remaining variables had individual *p*-values smaller than 0.05. *F*-tests were used to further compare the fits of the linear models and to analyse significant (disease or treatment) main effects in the final models. The statistical analyses were performed using the Statistica software (TIBCO Software Inc. 2017, Palo Alto, California, USA) for Windows.

5. RESULTS

General characteristics of the study groups

The studies were carried out on carefully selected FEP patients and in a CS group in order to exclude FEP patients with substance-induced psychosis or psychosis due to their general medical condition and to exclude CS with psychiatric disorders or among their close relatives. The application of Shapiro-Wilk test indicated that age and BMI followed normal distributions, but the values of ACs, inflammatory, and OxS markers had non-normal distributions ($p < 0.05$). There were no statistically significant differences between the antipsychotic-naïve FEP patients and CS in terms of age ($t_{(73)} = 0.49$, $p = 0.62$) and gender ($\chi^2_{(1)} = 1.08$, $p = 0.30$), or mean (± s.d.) scores of BMI (22.6 ± 2.9 and 23.0 ± 3.1, respectively; $t_{(73)} = –0.69$, $p = 0.49$). During the 7-month antipsychotic treatment, positive symptom ($Z = 5.16$, $p < 0.000001$), negative symptom ($Z = 5.23$, $p < 0.000001$), general symptom ($Z = 5.18$, $p < 0.000001$) and total symptom ($Z = 5.23$, $p < 0.000001$) scores demonstrated a significant positive decline. The 7-month treatment caused a significant change in BMI ($t_{(35)} = –8.07$, $p < 0.000001$). Mean BMI gain at 7 months follow-up was 2.97 kg/m^2 (±2.21). In addition, the difference in tobacco use (8 patients [21.1%] versus 7 controls [18.9%]) was not statistically significant ($\chi^2_{(1)} = 0.05$, $p = 0.82$).

5.1. Profiling of acylcarnitines in first-episode psychosis before and after seven-month antipsychotic treatment (Paper I)

Based on the evident impact of ACs on lipid metabolism, FAO and insulin sensitivity, as well as their associations with inflammatory responses, a well-characterized cohort of antipsychotic-naïve FEP patients and CS was used to profile CARN and ACs in their blood samples.

5.1.1. Acylcarnitine profile alterations in first-episode psychosis patients before and after seven-month antipsychotic treatment

The whole set of 39 ACs together with CARN were measured in FEP patients and CS (Table 1). Mann-Whitney *U*-test and Wilcoxon matched pairs test were first run to report differences in AC baseline levels between the groups (FEP patients vs. CS) and within the FEP group (before and after 7-month anti-psychotic treatment).

Twenty-four out of 39 ACs exhibited shifts in FEP patients at baseline compared to CS, but only eight of them (C14:1, C16, C16:1, C16:1-OH, C18:1, C18:2, C3, C6[C4:1-DC]) remained after the Bonferroni correction for multiple

comparisons ($p \leq 0.001$) and demonstrated large effect sizes (Table 1). All of the above-mentioned ACs were increased, except for C3 which was decreased.

Thereafter, the impact of treatment on ACs levels was analysed (Table 2); 4 ACs (C16, C18:1, C18:2, C3) were statistically significant and also reflected large effect sizes. As a result of antipsychotic treatment, 3 out of these 4 ACs demonstrated a decrease in their levels, except for C3 which was increased.

Table 1. Identification of differences in serum acylcarnitine levels (μmoles) between first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics) and control subjects (CS).

Biomarkers	**CS**	**FEP at baseline**	**Z-value[a]**	***p*-value[a]**	**Effect size (η^2)**
	Median (min–max) (N=37)	**Median (min–max) (N=38)**			
C0_Carnitine	32.20 (17.30–52.70)	33.30 (18.30–46.60)	0.17	0.87	–
C10_ Decanoyl-carnitine	0.28 (0.15–0.45)	0.31 (0.17–0.87)	– 2.13	0.03	0.06
C10:1_Decenoyl-carnitine	0.13 (0.08–0.23)	0.14 (0.06–0.30)	– 0.96	0.34	–
C10:2_Decadienyl-carnitine	0.06 (0.04–0.10)	0.06 (0.04–0.09)	0.54	0.59	–
C12_Dodecanoyl-carnitine	0.11 (0.06–0.18)	0.12 (0.06–0.32)	–2.29	0.02	0.07
C12-DC_Dodecanedioyl-carnitine	0.12 (0.11–0.14)	0,13 (0.08–0.15)	–0.59	0.56	–
C12:1_Dodecenoyl-carnitine	0.12 (0.07–0.19)	0.13 (0.07–0.29)	–2.13	0.03	0.06
C14_Tetradecanoyl-carnitine	0.03 (0.01–0.04)	0.03 (0.02–0.05)	–2.44	0.02	0.08
C14:1_Tetradecenoyl-carnitine	0.04 (0.02–0.11)	0.06 (0.03–0.15)	–3.34	**0.0008**	**0.15**
C14:1-OH_Hydroxytetra-decenoyl-carnitine	0.02 (0.01–0.02)	0.02 (0.01–0.03)	–2.45	0.01	0.08
C14:2_Tetradecadienyl-carnitine	0.02 (0.01–0.05)	0.02 (0.01–0.07)	–3.10	0.002	0.13
C14:2-OH_Hydroxytetra-decadienyl-carnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	–0.18	0.86	–
C16_Hexadecanoyl-carnitine	0.09 (0.04–0.12)	0.12 (0.06–0.20)	–4.28	**0.00002**	**0.24**
C16-OH_Hydroxyhexa-decanoyl-carnitine	0.01 (0.01–0.03)	0.02 (0.01–0.03)	–2.34	0.02	0.07
C16:1_Hexa-decenoyl-carnitine	0.02 (0.02–0.04)	0.03 (0.02–0.06)	–4.51	**0.000007**	**0.27**
C16:1-OH_Hydroxyhexa-decenoyl-carnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	–3.42	**0.0006**	**0.16**

Biomarkers	CS	FEP at baseline	Z-value[a]	*p*-value[a]	Effect size (I^2)
	Median (min–max) (N=37)	Median (min–max) (N=38)			
C16:2_Hexadeca-dienylcarnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	–1.53	0.13	–
C16:2-OH_Hydroxyhexa-decadienyl-carnitine	0.03 (0.02–0.04)	0.03 (0.02–0.04)	1.08	0.28	–
C18_Octadecanoyl-carnitine	0.04 (0.02–0.07)	0.05 (0.03–0.09)	–2.92	0.004	0.11
C18:1_Octadecenoyl-carnitine	0.09 (0.05–0.15)	0.13 (0.05–0.23)	–4.86	**0.000001**	**0.32**
C18:1-OH_Hydroxyocta-decenoyl-carnitine	0.02 (0.01–0.05)	0.03 (0.02–0.05)	–2.02	0.04	0.05
C18:2_Octadecadienyl-carnitine	0.03 (0.01–0.05)	0.04 (0.02–0.07)	–3.68	**0.0002**	**0.18**
C2_Acetylcarnitine	3.96 (1.78–5.96)	4.33 (1.73–14.00)	–0.67	0.50	–
C3_Propionyl-carnitine	0.31 (0.13–0.61)	0.23 (0.14–0.49)	3.72	**0.0002**	**0.19**
C3-DC(C4-OH)_Malonyl-carnitine (Hydroxy-butyrylcarnitine)	0.04 (0.03–0.07)	0.05 (0.03–0.25)	–2.95	0.003	0.12
C5-OH(C3-DC-M)_ Hydroxyvaleryl-carnitine (Methyl-malonylcarnitine)	0.06 (0.04–0.09)	0.06 (0.04–0.11)	–0.29	0.78	–
C3-OH_Hydroxy-propionyl-carnitine	0.04 (0.03–0.05)	0.04 (0.03–0.07)	0.88	0.38	–
C3:1_Propenoyl-carnitine	0.03 (0.02–0.04)	0.03 (0.02–0.05)	–0.80	0.42	–
C4_Butyryl-carnitine	0.18 (0.12–0.30)	0.17 (0.10–0.32)	2.63	0.008	0.09
C4:1_Butenylcarnitine	0.05 (0.03–0.06)	0.05 (0.03–0.06)	–1.71	0.09	–
C6(C4:1-DC)_ Hexanoylcarnitine (Fumarylcarnitine)	0.03 (0.02–0.04)	0.03 (0.02–0.05)	–3.43	**0.0006**	**0.16**
C5_Valeryl-carnitine	0.17 (0.10–0.29)	0.14 (0.10–0.31)	2.73	0.006	0.10
C5-DC(C6-OH)_Glutaryl-carnitine (Hydroxyhexanoyl-carnitine)	0.02 (0.01–0.04)	0.03 (0.02–0.04)	–2.11	0.04	0.06
C5-M-DC_Methylglutaryl-carnitine	0.04 (0.03–0.06)	0.04 (0.03–0.06)	–0.44	0.66	–
C5:1_Tiglylcarnitine	0.08 (0.05–0.12)	0.08 (0.05–0.11)	–0.17	0.87	–
C5:1-DC_Glutaconyl-carnitine	0.03 (0.02–0.04)	0.03 (0.02–0.03)	–2.23	0.03	0.07

Biomarkers	CS	FEP at baseline	Z-value[a]	*p*-value[a]	Effect size (I^2)
	Median (min–max) (N=37)	Median (min–max) (N=38)			
C6:1_Hexenoyl-carnitine	0.009 (0.006–0.01)	0.01 (0.007–0.01)	–1.27	0.21	–
C7-DC_Pimelylcarnitine	0.03 (0.02–0.04)	0.03 (0.02–0.06)	–1.75	0.08	–
C8_Octanoylcarnitine	0.13 (0.09–0.20)	0.14 (0.10–0.33)	–1.48	0.14	–
C9_Nonaylcarnitine	0.06 (0.03–0.12)	0.05 (0.03–0.08)	2.88	0.004	0.11
H1_Hexose	3907.00 (2335– 5533)	4291.50 (2802– 5918)	–2.59	0.01	0.09

Z-adjusted values according to Mann-Whitney *U*-test (first-episode psychosis patients before the treatment compared to CS); *p*-values ≤0.001 after the Bonferroni correction (bold) were considered statistically significant. Effect sizes were interpreted as medium and large, with corresponding eta-squared ranging from 0.06–0.13, and ≥0.14, respectively.

Table 2. Identification of differences in serum acylcarnitine levels (μmoles) between first-episode psychosis (FEP) patients at baseline and FEP patients after seven-month treatment with antipsychotics.

Biomarkers	FEP at Baseline	FEP after treatment	Z-value[b]	*p*-value[b]	Effect size (I^2)
	Median (min–max) (N=36)	Median (min–max) (N=36)			
C0_Carnitine	33.30 (18.30–46.60)	30.35 (15.80–58.40)	0.32	0.75	–
C10_ Decanoyl-carnitine	0.31 (0.17–0.87)	0.22 (0.12–1.08)	1.43	0.15	–
C10:1_Decenoyl-carnitine	0.14 (0.06–0.30)	0.13 (0.06–0.31)	0.80	0.42	–
C10:2_Decadienyl-carnitine	0.06 (0.04–0.09)	0.05 (0.04–0.10)	0.72	0.47	–
C12_Dodecanoyl-carnitine	0.12 (0.06–0.32)	0.09 (0.04–0.28)	1.71	0.09	–
C12-DC_Dodecanedioyl-carnitine	0.13 (0.08–0.15)	0.12 (0.10–0.16)	0.45	0.65	–
C12:1_Dodecenoyl-carnitine	0.13 (0.07–0.29)	0.12 (0.05–0.27)	1.63	0.10	–
C14_Tetradecanoyl-carnitine	0.03 (0.02–0.05)	0.02 (0.01–0.04)	2.59	0.01	0.09
C14:1_Tetradecenoyl-carnitine	0.06 (0.03–0.15)	0.04 (0.02–0.16)	2.53	0.01	0.09
C14:1-OH_Hydroxytetra-decenoyl-carnitine	0.02 (0.01–0.03)	0.01 (0.01–0.03)	2.29	0.02	0.07

Biomarkers	FEP at Baseline	FEP after treatment	Z-value [b]	*p*-value [b]	Effect size (I^2)
	Median (min–max) (N=36)	Median (min–max) (N=36)			
C14:2_Tetradecadienyl-carnitine	0.02 (0.01–0.07)	0.02 (0.01–0.04)	2.75	0.006	0.11
C14:2-OH_Hydroxytetra-decadienyl-carnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	1.65	0.10	–
C16_Hexadecanoyl-carnitine	0.12 (0.06–0.20)	0.08 (0.04–0.15)	3.40	**0.0007**	**0.16**
C16-OH_Hydroxyhexa-decanoyl-carnitine	0.02 (0.01–0.03)	0.01 (0.01–0.03)	1.76	0.08	–
C16:1_Hexa-decenoyl-carnitine	0.03 (0.02–0.06)	0.02 (0.01–0.05)	3.05	0.002	0.13
C16:1-OH_Hydroxyhexa-decenoyl-carnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	2.62	0.009	0.10
C16:2_Hexadeca-dienylcarnitine	0.01 (0.01–0.02)	0.01 (0.01–0.02)	2.47	0.01	0.09
C16:2-OH_Hydroxyhexa-decadienyl-carnitine	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.70	0.48	–
C18_Octadecanoyl-carnitine	0.05 (0.03–0.09)	0.04 (0.02–0.06)	2.70	0.007	0.10
C18:1_ Octadecenoyl-carnitine	0.13 (0.05–0.23)	0.08 (0.04–0.17)	4.13	**0.00004**	**0.24**
C18:1-OH_Hydroxyocta-decenoyl-carnitine	0.03 (0.02–0.05)	0.02 (0.01–0.05)	1.38	0.17	–
C18:2_Octadecadienyl-carnitine	0.04 (0.02–0.07)	0.03 (0.02–0.05)	3.86	**0.0001**	**0.21**
C2_Acetylcarnitine	4.33 (1.73–14.00)	4.11 (2.24–7.72)	0.66	0.51	–
C3_Propionyl-carnitine	0.23 (0.14–0.49)	0.30 (0.14–0.62)	3.22	**0.001**	**0.15**
C3-DC(C4-OH)_Malonyl-carnitine (Hydroxy-butyrylcarnitine)	0.05 (0.03–0.25)	0.04 (0.03–0.07)	2.69	0.007	0.10
C5-OH(C3-DC-M)_ Hydroxyvaleryl-carnitine (Methyl-malonylcarnitine)	0.06 (0.04–0.11)	0.06 (0.05–0.12)	1.11	0.27	–
C3-OH_Hydroxy-propionyl-carnitine	0.04 (0.03–0.07)	0.04 (0.03–0.07)	0.05	0.96	–
C3:1_Propenoyl-carnitine	0.03 (0.02–0.05)	0.03 (0.02–0.06)	1.02	0.31	–
C4_Butyryl-carnitine	0.17 (0.10–0.32)	0.17 (0.10–0.31)	0.78	0.44	–
C4:1_Butenylcarnitine	0.05 (0.03–0.06)	0.05 (0.03–0.07)	0.86	0.39	–
C6(C4:1-DC)_ Hexa-noylcarnitine (Fumarylcarnitine)	0.03 (0.02–0.05)	0.02 (0.01–0.06)	2.22	0.03	0.07

Biomarkers	FEP at Baseline	FEP after treatment	Z-value [b]	*p*-value [b]	Effect size (I^2)
	Median (min–max) (N=36)	Median (min–max) (N=36)			
C5_Valeryl-carnitine	0.14 (0.10–0.31)	0.16 (0.10–0.39)	2.51	0.01	0.09
C5-DC(C6-OH)_Glutaryl-carnitine (Hydroxyhexanoyl-carnitine)	0.03 (0.02–0.04)	0.02 (0.01–0.04)	2.37	0.02	0.09
C5-M-DC_Methylglutaryl-carnitine	0.04 (0.03–0.06)	0.04 (0.02–0.05)	1.00	0.32	–
C5:1_Tiglylcarnitine	0.08 (0.05–0.11)	0.07 (0.04–0.12)	1.05	0.30	–
C5:1-DC_Glutaconyl-carnitine	0.03 (0.02–0.03)	0.02 (0.01–0.04)	0.92	0.36	–
C6:1_Hexenoyl-carnitine	0.01 (0.007–0.01)	0.009 (0.006–0.01)	1.43	0.15	–
C7-DC_Pimelylcarnitine	0.03 (0.02–0.06)	0.03 (0.01–0.05)	2.16	0.03	0.07
C8_Octanoylcarnitine	0.14 (0.10–0.33)	0.12 (0.07 –0.42)	1.18	0.24	–
C9_Nonaylcarnitine	0.05 (0.03–0.08)	0.06 (0.04–0.09)	1.83	0.07	–
H1_Hexose	4291.50 (2802– 5918)	4054.50 (2846–7189)	0.93	0.35	–

Z-values according to Wilcoxon matched pairs test (first-episode psychosis patients before the treatment compared to first-episode psychosis patients after the treatment); *p*-values less than or equal to 0.001 after the Bonferroni correction (bold) were considered statistically significant. Effect sizes were interpreted as medium and large, with corresponding eta-squared ranging from 0.06–0.13, and ≥0.14, respectively.

5.1.2. The profile of acylcarnitines specific for first-episode psychosis and seven-month antipsychotic treatment

An alternative methodological approach (GLM) was applied to confirm the existence of significant main effects of the disease and treatment on the levels of ACs. Important co-variates (gender, smoking status, age) were included in the further analyses. After applying GLM, the levels of 22 ACs (and hexose) demonstrated statistically significant differences, and the most prominent difference emerged in five ACs levels (C14:1, C16, C16:1, C18:1 and C3) out of which 4 ACs (C14:1, C16, C16:1, C18:1) showed an increase in their levels and C3 showed a decrease when comparing drug-naïve FEP patients and CS (Table 3).

A positive treatment effect occurred in relation to 14 ACs levels, the most significant among them being a decrease in C18:1 level when FEP patients were

compared before and after treatment (Table 4). Interestingly, no differences in AC levels were detected by using GLM between CS and post-treatment FEP patients (Table 5).

Table 3. Comparison of acylcarnitine serum levels between first-episode psychosis (FEP) patients at baseline (before the treatment with antipsychotics) and control subjects (CS).

Biomarkers	**ß**	**ß (95 % CI)**	***t*-value**	***p*-value**
C0_Carnitine	–0.06	–0.30, 0.17	–0.54	0.59
C10_Decanoylcarnitine	0.32	0.09, 0.54	2.82	**0.006**
C10:1_Decenoylcarnitine	0.15	–0.08, 0.39	1.28	0.21
C10:2_Decadienylcarnitine	–0.09	–0.32, 0.14	–0.80	0.43
C12_Dodecanoylcarnitine	0.28	0.06, 0.51	2.48	**0.02**
C12-DC_Dodecanedioylcarnitine	–0.04	–0.26, 0.19	–0.31	0.76
C12:1_Dodecenoylcarnitine	0.25	0.03, 0.48	2.23	**0.03**
C14_Tetradecanoylcarnitine	0.30	0.08, 0.52	2.73	**0.008**
C14:1_Tetradecenoylcarnitine	0.43	0.22, 0.64	4.08	**0.0001**
C14:1-OH_Hydroxytetradecenoylcarnitine	0.29	0.06, 0.52	2.55	**0.01**
C14:2_Tetradecadienylcarnitine	0.39	0.17, 0.61	3.56	**0.0007**
C14:2-OH_Hydroxytetradecadienylcarnitine	0.004	–0.23, 0.24	0.03	0.98
C16_Hexadecanoylcarnitine	0.48	0.28, 0.69	4.63	**0.00002**
C16-OH_Hydroxyhexadecanoylcarnitine	0.25	0.02, 0.48	2.19	**0.03**
C16:1_Hexadecenoylcarnitine	0.55	0.36, 0.74	5.81	**0.000001**
C16:1-OH_Hydroxyhexadecenoylcarnitine	0.41	0.20, 0.62	3.93	**0.0002**
C16:2_Hexadecadienylcarnitine	0.18	–0.06, 0.41	1.52	0.13
C16:2-OH_Hydroxyhexadecadienylcarnitine	–0.12	0.36, 0.12	–1.02	0.31
C18_Octadecanoylcarnitine	0.33	0.11, 0.56	2.93	**0.005**
C18:1_Octadecenoylcarnitine	0.57	0.37, 0.76	5.77	**0.000001**
C18:1-OH_Hydroxyoctadecenoylcarnitine	0.20	–0.04, 0.43	1.70	0.09
C18:2_Octadecadienylcarnitine	0.42	0.21, 0.63	3.93	**0.0002**
C2_Acetylcarnitine	0.18	–0.04, 0.40	1.65	0.10
C3_Propionylcarnitine	–0.46	–0.67, –0.26	–4.51	**0.00003**
C3-DC(C4-OH)_Malonylcarnitine (Hydroxybutyrylcarnitine)	0.35	0.13, 0.57	3.14	**0.003**
C5-OH(C3-DC-M)_Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	0.08	–0.15, 0.31	0.70	0.49
C3-OH_Hydroxypropionylcarnitine	–0.02	–0.26, 0.22	–0.19	0.86
C3:1_Propenoylcarnitine	0.07	–0.17, 0.30	0.54	0.59
C4_Butyrylcarnitine	–0.36	–0.58, –0.15	–3.33	**0.001**
C4:1_Butenylcarnitine	0.21	–0.02, 0.44	1.80	0.08
C6(C4:1-DC)_Hexanoylcarnitine (Fumarylcarnitine)	0.42	0.20, 0.64	3.83	**0.0003**
C5_Valerylcarnitine	–0.30	–0.52, –0.08	–2.69	**0.009**
C5-DC(C6-OH)_Glutarylcarnitine	0.23	0.004, 0.45	2.03	**0.046**

Biomarkers	ß	ß (95 % CI)	*t*-value	*p*-value
(Hydroxyhexanoylcarnitine)				
C5-M-DC_Methylglutarylcarnitine	0.05	–0.18, 0.29	0.45	0.66
C5:1_Tiglylcarnitine	0.01	–0.23, 0.25	0.09	0.93
C5:1-DC_Glutaconylcarnitine	0.18	–0.05, 0.40	1.53	0.13
C6:1_Hexenoylcarnitine	0.14	–0.09, 0.38	1.20	0.24
C7-DC_Pimelylcarnitine	0.22	–0.01, 0.45	1.91	0.06
C8_Octanoylcarnitine	0.25	0.02, 0.48	2.19	**0.03**
C9_Nonaylcarnitine	–0.37	–0.59, –0.15	–3.32	**0.001**
H1_Hexose	0.28	0.06, 0.50	2.49	**0.02**

ß: regression coefficients; CI: confidence intervals; *p*-values (derived from GLM analysis); significance of $\log_{10}$-transformed values in acylcarnitine levels in the disease, adjusted for gender, age and smoking status. Significant *t*-values ($p < 0.05$) are marked in bold.

Table 4. Effects of seven-month treatment with antipsychotics on metabolite levels among the first-episode psychosis (FEP) patient group.

Biomarkers	ß	ß (95 % CI)	*t*-value	*p*-value
C0_Carnitine	0.08	–0.24, 0.40	0.52	0.61
C10_Decanoylcarnitine	0.21	–0.09, 0.50	1.40	0.17
C10:1_Decenoylcarnitine	0.06	–0.24, 0.36	0.40	0.69
C10:2_Decadienylcarnitine	0.09	–0.21, 0.39	0.61	0.54
C12_Dodecanoylcarnitine	0.27	–0.02, 0.56	1.87	0.07
C12-DC_Dodecanedioylcarnitine	–0.16	–0.47, 0.15	–1.03	0.31
C12:1_Dodecenoylcarnitine	0.17	–0.13, 0.47	1.11	0.27
C14_Tetradecanoylcarnitine	0.38	0.09, 0.67	2.64	**0.01**
C14:1_Tetradecenoylcarnitine	0.41	0.14, 0.68	3.02	**0.004**
C14:1-OH_Hydroxytetradecenoylcarnitine	0.34	0.05, 0.64	2.32	**0.02**
C14:2_Tetradecadienylcarnitine	0.41	0.13, 0.69	2.94	**0.005**
C14:2-OH_Hydroxytetradecadienylcarnitine	0.23	–0.08, 0.53	1.48	0.15
C16_Hexadecanoylcarnitine	0.47	0.20, 0.74	3.44	**0.001**
C16-OH_Hydroxyhexadecanoylcarnitine	0.29	–0.01, 0.59	1.91	0.06
C16:1_Hexadecenoylcarnitine	0.44	0.19, 0.70	3.42	**0.001**
C16:1-OH_Hydroxyhexadecenoylcarnitine	0.43	0.15, 0.71	3.06	**0.003**
C16:2_Hexadecadienylcarnitine	0.31	0.02, 0.61	2.10	**0.04**
C16:2-OH_Hydroxyhexadecadienylcarnitine	–0.16	–0.47, 0.16	–0.99	0.33
C18_Octadecanoylcarnitine	0.38	0.08, 0.68	2.51	**0.02**
C18:1_Octadecenoylcarnitine	0.55	0.31, 0.80	4.47	**0.00003**
C18:1-OH_Hydroxyoctadecenoylcarnitine	0.33	0.04, 0.63	2.25	**0.03**
C18:2_Octadecadienylcarnitine	0.47	0.20, 0.74	3.51	**0.0008**
C2_Acetylcarnitine	0.03	–0.27, 0.32	0.17	0.87
C3_Propionylcarnitine	–0.39	–0.68, –0.10	–2.66	**0.01**
C3-DC(C4-OH)_Malonylcarnitine	0.38	0.10, 0.66	2.71	**0.009**

Biomarkers	ß	ß (95 % CI)	*t*-value	*p*-value
(Hydroxybutyrylcarnitine)				
C5-OH(C3-DC-M)_Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	0.07	–0.24, 0.38	0.48	0.64
C3-OH_Hydroxypropionylcarnitine	0.14	–0.17, 0.45	0.90	0.37
C3:1_Propenoylcarnitine	0.16	–0.16, 0.47	1.00	0.32
C4_Butyrylcarnitine	–0.17	–0.49, 0.14	–1.12	0.27
C4:1_Butenylcarnitine	0.23	–0.08, 0.55	1.50	0.14
C6(C4:1-DC)_Hexanoylcarnitine (Fumarylcarnitine)	0.29	–0.01, 0.59	1.99	0.05
C5_Valerylcarnitine	–0.27	–0.57, 0.03	–1.79	0.08
C5-DC(C6-OH)_Glutarylcarnitine (Hydroxyhexanoylcarnitine)	0.27	–0.02, 0.56	1.88	0.07
C5-M-DC_Methylglutarylcarnitine	0.17	–0.14, 0.48	1.10	0.28
C5:1_Tiglylcarnitine	0.06	–0.25, 0.37	0.42	0.68
C5:1-DC_Glutaconylcarnitine	0.12	–0.18, 0.42	0.80	0.43
C6:1_Hexenoylcarnitine	0.03	–0.27, 0.33	0.20	0.84
C7-DC_Pimelylcarnitine	0.28	–0.02, 0.58	1.89	0.06
C8_Octanoylcarnitine	0.16	–0.14, 0.46	1.06	0.29
C9_Nonaylcarnitine	–0.19	–0.49, 0.11	–1.26	0.21
H1_Hexose	0.17	–0.13, 0.48	1.13	0.26

ß: regression coefficients; CI: confidence intervals; *p*-values (derived from GLM repeated measure); significance of $\log_{10}$-transformed values in acylcarnitine levels in the patient group before treatment compared with the biomarker values measured after 7-month treatment with antipsychotics, adjusted for gender, and smoking status. Significant *t*-values ($p < 0.05$) are marked in bold.

Table 5. Metabolite levels in first-episode psychosis (FEP) patients after seven-month treatment with antipsychotics compared to control subjects (CS).

Biomarkers	ß	ß (95 % CI)	*t*-value	*p*-value
C0_Carnitine	–0.11	–0.34, 0.13	–0.93	0.36
C10_Decanoylcarnitine	–0.03	–0.27, 0.20	–0.29	0.77
C10:1_Decenoylcarnitine	–0.03	–0.26, 0.21	–0.22	0.83
C10:2_Decadienylcarnitine	–0.16	–0.39, 0.08	–1.35	0.18
C12_Dodecanoylcarnitine	–0.10	–0.33, 0.13	–0.84	0.40
C12-DC_Dodecanedioylcarnitine	–0.02	–0.26, 0.23	–0.14	0.89
C12:1_Dodecenoylcarnitine	–0.05	–0.29, 0.19	–0.40	0.69
C14_Tetradecanoylcarnitine	–0.16	–0.39, 0.08	–1.31	0.20
C14:1_Tetradecenoylcarnitine	–0.10	–0.33, 0.13	–0.89	0.38
C14:1-OH_Hydroxytetradecenoylcarnitine	–0.11	–0.34, 0.13	–0.92	0.36
C14:2_Tetradecadienylcarnitine	–0.16	–0.38, 0.07	–1.40	0.17
C14:2-OH_Hydroxytetradecadienylcarnitine	–0.22	–0.45, 0.02	–1.86	0.07
C16_Hexadecanoylcarnitine	–0.03	–0.27, 0.20	–0.28	0.79
C16-OH_Hydroxyhexadecanoylcarnitine	0.07	–0.17, 0.31	0.59	0.56

Biomarkers	ß	ß (95 % CI)	*t*-value	*p*-value
C16:1_Hexadecenoylcarnitine	0.003	–0.24, 0.24	0.02	0.98
C16:1-OH_Hydroxyhexadecenoylcarnitine	0.06	–0.19, 0.30	0.45	0.65
C16:2_Hexadecadienylcarnitine	–0.18	–0.42, 0.05	–1.59	0.12
C16:2-OH_Hydroxyhexadecadienylcarnitine	–0.08	–0.31, 0.16	–0.63	0.53
C18_Octadecanoylcarnitine	0.001	–0.24, 0.24	0.01	0.99
C18:1_Octadecenoylcarnitine	–0.07	–0.31, 0.17	–0.61	0.54
C18:1-OH_Hydroxyoctadecenoylcarnitine	–0.03	–0.26, 0.21	–0.23	0.82
C18:2_Octadecadienylcarnitine	–0.08	–0.31, 0.14	–0.74	0.46
C2_Acetylcarnitine	0.13	–0.10, 0.36	1.11	0.27
C3_Propionylcarnitine	–0.08	–0.31, 0.16	–0.64	0.53
C3-DC(C4-OH)_Malonylcarnitine (Hydroxybutyrylcarnitine)	–0.01	–0.24, 0.23	–0.04	0.97
C5-OH(C3-DC-M)_Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	0.07	–0.17, 0.30	0.58	0.56
C3-OH_Hydroxypropionylcarnitine	–0.02	–0.26, 0.22	0.20	0.84
C3:1_Propenoylcarnitine	0.02	–0.21, 0.25	0.17	0.86
C4_Butyrylcarnitine	–0.22	–0.45, 0.02	–1.84	0.07
C4:1_Butenylcarnitine	0.12	–0.11, 0.35	1.02	0.31
C6(C4:1-DC)_Hexanoylcarnitine (Fumarylcarnitine)	–0.01	–0.25, 0.23	–0.10	0.92
C5_Valerylcarnitine	–0.01	–0.24, 0.23	–0.06	0.95
C5-DC(C6-OH)_Glutarylcarnitine (Hydroxyhexanoylcarnitine)	–0.09	–0.32, 0.14	–0.76	0.45
C5-M-DC_Methylglutarylcarnitine	–0.09	–0.33, 0.15	–0.74	0.46
C5:1_Tiglylcarnitine	–0.08	–0.32, 0.16	–0.68	0.50
C5:1-DC_Glutaconylcarnitine	0.02	–0.22, 0.26	0.15	0.88
C6:1_Hexenoylcarnitine	–0.04	–0.27, 0.20	–0.31	0.76
C7-DC_Pimelylcarnitine	–0.17	–0.40, 0.06	–1.45	0.15
C8_Octanoylcarnitine	–0.02	–0.26, 0.22	–0.15	0.88
C9_Nonaylcarnitine	–0.13	–0.37, 0.11	–1.08	0.28
H1_Hexose	0.20	–0.03, 0.43	1.72	0.09

ß: regression coefficients; CI: confidence intervals; *p*-values (derived from GLM analysis); significance of $\log_{10}$-transformed values in acylcarnitine levels in the first-episode patient group after 7-month treatment with antipsychotics compared to control subjects, adjusted for gender, age and smoking status.

5.1.3. Ratio of CARN to LCACs and SCACs

Calculation of the ratio of CARN to LCACs and SCACs was based on raw data. The SCACs to CARN ratio in drug-naïve FEP patients showed a significant decrease in C3 (Mann Whitney *U*-test, $Z = 4.24$, $p = 0.00002$) and C5 ($Z = 2.38$, $p = 0.018$) (Figure 1), whereas, CPT-1, reflecting the ratio of LCACs to CARN, demonstrated increased accumulation of C14, C16, C18 ($Z = 3.42$, $p = 0.0006$). Treatment with antipsychotic drugs eliminated all the above-mentioned shifts. The levels of C3 (Wilcoxon matched paired tests, $Z = 4.10$, $p = 0.00004$) and C5 ($Z = 2.38$, $p = 0.017$) were significantly increased compared with CARN (Figure 1). By contrast, CPT-1 showed a tendency of reduction in LCACs levels ($Z = 2.19$, $p = 0.029$) compared with CARN.

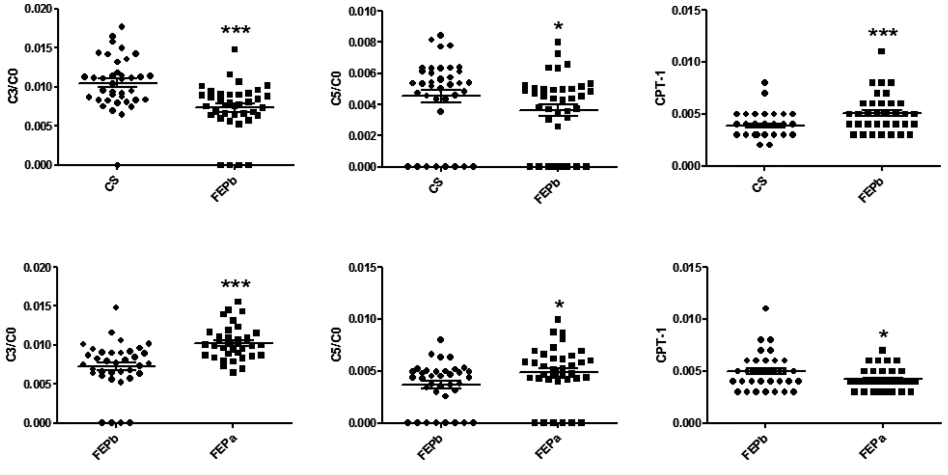

Figure 1. The ratio of short-chain acylcarnitines (SCACs) and long-chain acylcarnitines (LCACs) to carnitine (CARN) in FEP patients before and after antipsychotic treatment. CS: control subjects; FEPb: first-episode psychosis (FEP) patients at baseline (before the treatment); FEPa: FEP patients after the treatment with antipsychotic drugs; CPT-1: the ratio of LCACs to CARN; CS versus FEPb: Mann-Whitney *U*-test: * – $p < 0.05$; *** – $p < 0.001$; FEPb versus FEPa: Wilcoxon matched pairs' test: * – $p < 0.05$; *** – $p < 0.001$.

5.2. Selected inflammatory biomarkers in first-episode psychosis before and after seven-month antipsychotic treatment (Paper II)

This study focused on the status of selected inflammatory biomarkers (ferritin, IL-6, IL-1α, TNF-α, and PAI-1) in antipsychotic-naïve FEP patients at baseline compared to CS and analysed the change of inflammatory markers in FEP patients after 7-month antipsychotic treatment.

5.2.1. Differences in the levels of selected inflammatory biomarkers between antipsychotic-naïve first-episode psychosis patients and control subjects

The analysis of inflammatory biomarkers (Mann-Whitney *U*-test, raw data) showed a significant increase in ferritin, PAI-1, and IL-6 in antipsychotic-naïve FEP patients vs CS (Table 6). Based on this study sample, group differences for the above-mentioned biomarkers demonstrated medium effect sizes.

Table 6. Comparison of selected inflammatory biomarker levels between first-episode psychosis (FEP) patients at baseline and control subjects (CS).

Inflammatory Biomarkers	CS	FEP at baseline	Z-value	*p*-value	Effect size η^2
	Median (min–max)	Median (min–max)			
Ferritin	22.1 (1.22–185)	56.0 (4.26–239)	2.86	**0.004***	0.11
IL-6	0.53 (0.23–1.54)	0.84 (0.12–8.64)	2.53	**0.01***	0.09
IL-1α	0.32 (0.20–1.67)	0.30 (0.000–1.78)	–1.29	0.20	–
TNF-α	5.17 (3.42–8.73)	5.43 (2.92–10.7)	0.13	0.90	–
PAI-1	21.4 (7.57–49.9)	25.7 (8.92–48.6)	2.75	**0.006***	0.10

Data presented in pg/mL as medians (range). Z-values according to Mann-Whitney *U*-test (FEP patients before treatment compared to CS).
IL-1 α, IL-6: interleukins; TNF-α: tumour necrosis factor-α; PAI-1: plasminogen activator inhibitor-1; CS: control subjects.
**p*-values: adjusted with the Bonferroni correction of alpha ($0.05/5 \leq 0.01$).

5.2.2. Effects of antipsychotic drugs on inflammatory biomarkers

Seven-month antipsychotic treatment had a significant impact on several inflammatory biomarkers in FEP patients (Table 7) but the strongest decline was established for ferritin (p=0.00003), which showed a large effect. Changes were also revealed in the levels of IL-1α (p=0.01) as well as in IL-6 (p=0.03) and PAI-1 (p=0.03), which demonstrated medium-size effects in decline.

Table 7. Comparison of selected inflammatory biomarkers levels between first-episode psychosis (FEP) patients at baseline and after 7-month treatment with antipsychotics.

Biomarkers	FEP baseline	FEP after treatment	Z-value	p-value	Effect size η^2
	Median (min–max)	Median (min–max)			
Ferritin	56.0 (4.26–239)	30.9 (4.75–150)	4.19	**0.00003***	0.25
IL-6	0.84 (0.12–8.64)	0.75 (0.23–1.64)	2.16	0.03	0.07
IL-1α	0.30 (0–1.78)	0.24 (0–1.77)	2.47	**0.01***	0.11
TNF-α	5.43 (2.92–10.73)	5.10 (2.84–9.30)	0.01	0.99	–
PAI-1	25.7 (8.92–48.6)	22.0 (7.06–57.1)	2.24	0.03	0.07

Data presented in pg/mL as medians (range). Z-values according to Wilcoxon matched pairs test (FEP patients, pre- and post-treatment timepoints, respectively); IL-1 α, IL-6: interleukins; TNF-α: tumour necrosis factor-α; PAI-1: plasminogen activator inhibitor-1. *p-values: adjusted with the Bonferroni correction of alpha ($0.05/5 \leq 0.01$).

5.2.3. Inflammatory biomarker levels in first-episode psychosis patients after seven-month treatment with antipsychotics compared to control subjects

After seven-month antipsychotic treatment the most prominent decrease was seen in IL-1α levels, which demonstrated a medium effect size compared to IL-1α levels in CS (Table 8). Elevated levels of ferritin, TNF-α and PAI-1 in the FEP group demonstrated a considerable positive decrease as a result of treatment and returned to the corresponding levels in CS.

Table 8. Comparison of inflammatory biomarker levels between control subjects (CS) and first-episode psychosis (FEP) patients after seven-month treatment with antipsychotics.

Biomarkers	CS	FEP after treatment	Z-value	*p*-value	Effect size η^2
	Median (min–max)	Median (min–max)			
Ferritin	22.1 (1.22–185)	30.9 (4.75–150)	1.04	0.30	–
IL-6	0.53 (0.23–1.54)	0.75 (0.23–1.64)	1.74	0.08	–
IL-1α	0.32 (0.20–1.67)	0.24 (0–1.77)	–2.88	**0.004***	0.11
TNF-α	5.17 (3.42–8.73)	5.10 (2.84–9.30)	0.31	0.76	–
PAI-1	21.4 (7.57–49.9)	22.0 (7.06–57.1)	0.79	0.43	–

Data presented in pg/mL as medians (range). Z-adjusted values according to Mann-Whitney *U*-test (FEP patients after treatment compared to CS).
IL-1 α, IL-6: Interleukins; TNF-α: tumour necrosis factor-α; PAI-1: plasminogen activator inhibitor- 1.
**p*-values: adjusted with the Bonferroni correction of alpha ($0.05/5 \leq 0.01$).

5.3. Oxidative stress status in first-episode psychosis before and after seven-month antipsychotic treatment (Paper III)

This study was carried out to compare the OxS status [serum total antioxidant capacity (TAC), total level of peroxides (TPX), oxidative stress index (OSI), ratio of oxidized methionine (Met-SO) to methionine (Met)] between antipsychotic-naïve FEP patients and individuals without history of psychiatric disorders, i.e. CS.

5.3.1. Differences in the levels of oxidative stress markers among antipsychotic-naïve first-episode psychosis patients and control subjects

FEP patients compared to CS did not show any differences regarding OxS-related parameters (TPX, TAC, OSI), Met-SO and Met and Met-SO/Met ratio before treatment (Table 9, Figures 2A and B).

Table 9. Comparison of oxidative stress markers (OxS) between first-episode psychosis (FEP) patients at baseline and control subjects (CS), as well as FEP patients at baseline and after seven months of treatment with antipsychotics.

OxS markers	CS	FEP before treatment	FEP after treatment	Z-value[A]	*p*-value[A]	Z-value[B]	*p*-value[B]
	Median (min–max)	Median (min–max)	Median (min–max)				
TAC	1.43 (0.92–2.08)	1.42 (0.79–2.19)	1.47 (1.06–2.43)	–1.15	0.25	1.56	0.12
TPX	333 (101–737)	380 (167–1358)	289 (88–916)	1.03	0.30	2.20	0.03
OSI	21.9 (6.16–53.8)	24.4 (11.4–92.0)	19.3 (6.03–67.8)	1.32	0.19	2.56	0.01
Met	9.08 (4.43–35.2)	7.75 (4.46–26.3)	12.5 (4.53–33.5)	0.80	0.43	2.50	0.01
Met-SO	10.8 (3.04–23.1)	10.4 (2.11–24.9)	8.72 (1.69–20.3)	–0.98	0.33	2.05	0.04
Met-SO/ Met	1.44 (0.16–4.29)	1.35 (0.11–4.39)	0.66 (0.05–3.54)	–0.86	0.39	2.15	0.03

All units presented as medians (range): TAC in mmol Trolox Eq/L unit, TPX in µmol H_2O_2 Eq/L unit, OSI in percent ratio, Met and Met-SO in µmol, Met-SO/Met as ratio.
Z-values[A] according to Mann-Whitney *U*-test (FEP patients before treatment compared to CS).
Z-values[B] according to Wilcoxon matched pairs test (FEP before treatment compared to FEP after treatment). TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.

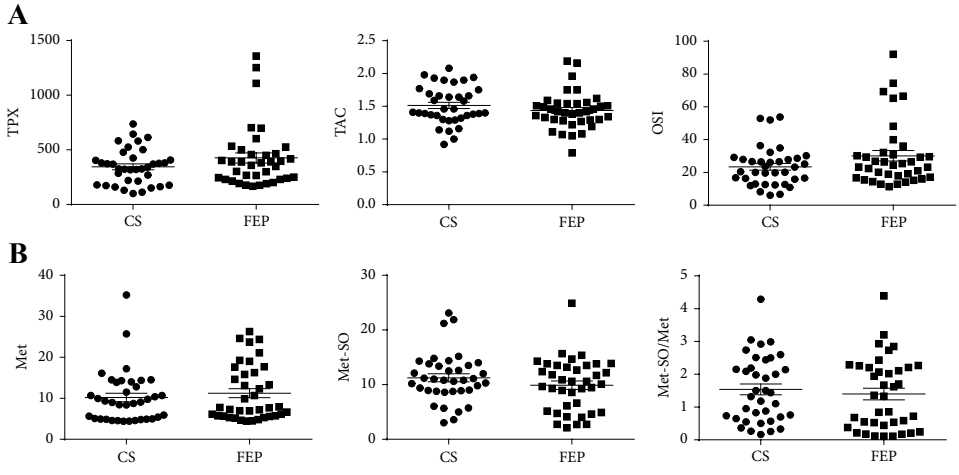

Figure 2. The changes in TPX, TAC and OSI (A) and Met, Met-SO, and Met-SO/Met (B) due to FEP (Wilcoxon signed rank test). FEP: first-episode psychosis; CS: control subjects; TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.

A multivariate GLM analysis was used to reveal the potential effect of FEP on the combination of OxS markers. The overall difference between the groups is presented in Table 10. The main effect of FEP was revealed in OSI level ($t_{(5,64)} = 2.26$, $p = 0.03$, $R_{adj}^2 = 0.17$) and was affected by male gender ($t_{(5,64)} = -3.32$, $p = 0.001$). Nevertheless, there was no statistically significant correlation between the group status and gender regarding OSI level. Considering the model-based level, there was a medium-size effect of the disease (before the treatment) on the OxS markers (partial η^2=0.13, $F_{(5,64)} = 1.9$, $p = 0.11$).

Table 10. Regression coefficients (β) and significance of $\log_{10}$-transformed values of the oxidative stress (OxS) markers in first-episode psychosis.

OxS markers	β	β (95 % CI)	*t*-value	*p*-value
TAC	–0.13	–0.37–0.11	–1.10	0.28
TPX	0.21	–0.02–0.43	1.82	0.07
OSI	0.25	0.03–0.47	2.26	0.03
Met	0.08	–0.15–0.31	0.70	0.49
Met-SO	–0.18	–0.41– 0.05	–1.58	0.12
Met-SO/ Met	–0.15	–0.37–0.08	–1.28	0.21

ß: regression coefficients; CI: Confidence intervals; TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.

5.3.2. The effect of antipsychotic treatment on the levels of biomarkers in first-episode psychosis

Comparison of FEP patients before and after seven-month antipsychotic therapy revealed a significant and positive decrease in TPX and OSI levels (Table 9, Figure 3A), as well as a positive increase in Met level and a decrease in Met-SO and Met-SO/Met (Table 11, Figure 3B).

In further analyses the impact of treatment on OxS levels was evaluated. Repeated measures GLM was used to compare the main effects of the 7-month antipsychotic treatment on the concentration of serum biomarkers. The effect of treatment is demonstrated in Table 11. Considering all measured OxS markers, the levels of TAC, Met, Met-SO, and Met-SO/Met did not differ between pre- and post-treatment conditions, whereas a decrease over time was detected in the serum levels of TPX ($p = 0.04$), and OSI ($p = 0.01$). These results confirm that treatment with antipsychotics has a positive impact on the OxS markers' levels during the early phase of the psychotic disease. The size of the effect of treatment (partial η^2) on the OxS markers was 0.17 ($F_{(5,64)} = 2.00$, $p = 0.08$).

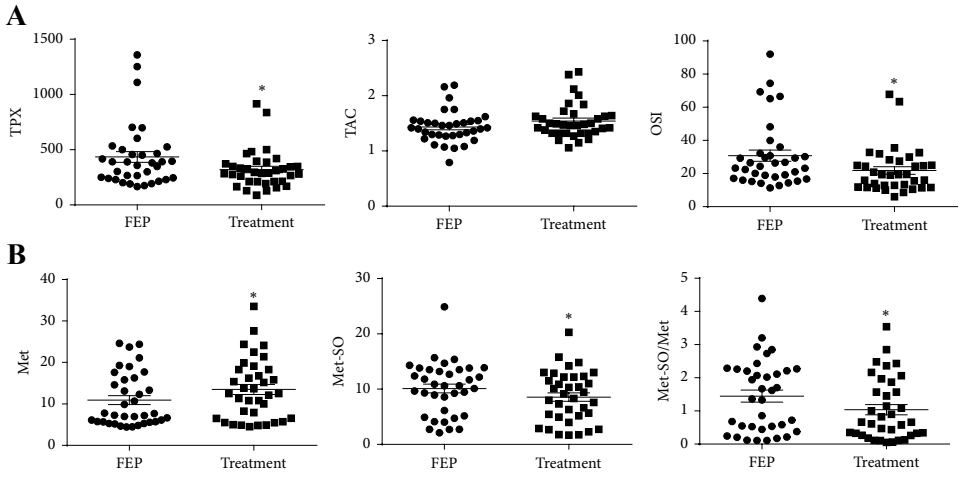

Figure 3. The changes in TPX, TAC and OSI (A) and Met, Met-SO, and Met-SO/Met (B) due to FEP and antipsychotic treatment. *$p < 0.05$ (Wilcoxon signed rank test). FEP: first-episode psychosis; TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.

Table 11. The effect of seven-month antipsychotic treatment on the oxidative stress (OxS) markers in the first-episode patient group.

OxS markers	*ß*	*ß* (95 % CI)	*t*-value	*p*-value
TAC	–0.19	–0.42–0.05	–1.56	0.12
TPX	0.25	0.02–0.48	2.12	**0.04**
OSI	0.30	0.07–0.53	2.61	**0.01**
Met	–0.19	–0.43–0.05	–1.62	0.11
Met-SO	0.15	–0.10–0.38	1.21	0.23
Met-SO/ Met	0.18	–0.06–0.42	1.51	0.14

ß: regression coefficients; CI: Confidence intervals; significance of the $\log_{10}$-transformed values for the oxidative stress (OxS) markers in the first-episode patient group, pre- and post-treatment timepoints; TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.
$p < 0.05$ values are marked in bold

Furthermore, GLM was used to evaluate the FEP patients' post-treatment status regarding the levels of OxS markers compared to CS (adjusted for age, gender and smoking status). The levels of TAC, TPX and OSI in FEP patients were comparable with those of CS (Table 12).

On the other hand, 7-month treatment with antipsychotics caused a significant increase in Met ($p = 0.03$) as well as a decrease in Met-SO ($p = 0.02$) and Met-SO/Met ($p = 0.006$) levels in the FEP patient group compared to CS. These changes were associated with the effects of age. In particular, the effect of treatment was significantly associated with higher Met levels in younger patients ($t_{(5,63)} = –3.06$, $p = 0.003$) as well as with lower levels of serum Met-SO and Met-SO/Met in older patients ($t_{(5,63)} = 2.45$, $p = 0.02$; $t_{(5,63)} = 3.14$, $p = 0.003$, respectively).

Table 12. The effect of 7-month antipsychotic treatment on the oxidative stress (OxS) markers in the first-episode patient group compared to the control subjects.

OxS markers	*ß*	*ß* (95 % CI)	*t*-value	*p*-value
TAC	0.02	–0.22–0.26	0.17	0.87
TPX	–0.01	–0.24–0.21	–0.12	0.90
OSI	–0.02	–0.24–0.20	–0.19	0.85
Met	0.24	0.02–0.47	2.21	**0.03**
Met-SO	–0.32	–0.54–(–0.09)	–2.77	**0.007**
Met-SO/ Met	–0.31	–0.53–(–0.10)	–2.86	**0.006**

ß: regression coefficients; CI: Confidence intervals; significance for the $\log_{10}$-transformed values for the oxidative stress (OxS) markers in the first-episode patients' group after treatment compared to CS; TAC: total antioxidant capacity; TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine.
$p < 0.05$ values are marked in bold

Spearman rank correlation established a significant positive correlation of TPX with IL-1β ($\rho = 0.26$, $p = 0.03$) and of TAC with IL-1β ($\rho = 0.25$, $p = 0.04$) among the FEP patients. After treatment, a significant negative correlation was found between treatment and OSI ($\rho = –0.28$, $p = 0.02$) and positive correlation was found between BMI and TAC ($\rho = 0.31$, $p < 0.01$).

6. DISCUSSION

FEP can be seen as an intermediate state which has relevant implications for further clinical course, treatment and management of chronic psychotic disorders. Patients need to receive the best comprehensive science-based care in order to achieve the best quality of remission and to avoid or to diminish the number of future psychoses. Among others, psychiatric disorders have been shown to be related to a shift in the composition of brain lipids (i.e. phospholipids, PUFAs) (Horrobin 1998; Horrocks LA & Farooqui 2004; Yao *et al*. 2004), inflammation (Potvin *et al*. 2008; de Witte *et al*. 2014; Miller *et al*. 2011; Upthegrove *et al*. 2014) and OxS (Kaur & Cadenhead 2010; Noto *et al*. 2015; Sarandol *et al*. 2015). Therefore, the general aim of this thesis was profiling of ACs, inflammation and OxS in FEP before and after treatment, specifically collecting data on the relationships between inflammation and OxS status and alterations in ACs in FEP.

6.1. Acylcarnitines in first-episode psychosis before and after seven-month antipsychotic treatment (Paper I)

Antipsychotic treatment is known to have an impact on patient's body weight (including BMI), glycose and lipid metabolism and may also affect the profile of ACs. The impact of ACs on FAO, inflammation and insulin sensitivity is widely known (Adams *et al*. 2009; Mihalik *et al.* 2010). Therefore, altered mitochondrial homeostasis may change the level of ACs and their accumulation may indicate mitochondrial dysfunction (MitoDys) (Sampey *et al*. 2012; D'Souza *et al*. 2016). Consequently, it is crucial to study the contribution of CARN and ACs to the metabolic status of psychiatric patients (Reuter & Evans, 2012), as according to literature, chronic treatment with antipsychotic drugs impacts lipid metabolism (Misiak *et al*. 2017; McEvoy *et al*. 2013; Bobo *et al*. 2011; Kaddurah-Daouk & Krishnan, 2009) and it can hence also cause shifts in the ACs profile. It has been proposed that the plasma concentrations of ACs, particularly medium- and long-chain ACs, can predict the intracellular energy metabolism pattern and can be used as markers for metabolic dysfunction (Mai *et al*. 2013; Koves *et al*. 2008; Adams *et al*. 2009).

Our current lipidomic profiling demonstrated shifts in 24 ACs out of 39 in FEP patients compared to CS, although only 8 of them (C14:1, C16, C16:1, C16:1-OH, C18:1, C18:2, C3, C6(C4:1-OH)) remained after the Bonferroni correction for multiple comparisons and showed large effect sizes. After applying GLM for the same sample, 5 ACs demonstrated the most prominent shifts. Four ACs (C14:1, C16, C16:1 and C18:1) out of 5 were significantly elevated and one (C3) was substantially decreased in FEP patients compared to CS, which would allow to make the generalization that there is a shift towards an increase in LCACs and a decrease in SCACs.

Antipsychotic treatment for 7 months caused significant alterations in 14 metabolites in FEP patients, but only 4 ACs (C16, C18:1, C18:2, C3) remained after the Bonferroni correction for multiple comparisons and demonstrated large effect sizes. The levels of 3 of these ACs were significantly decreased (C16, C18:1, C18:2) and the level of C3 was significantly increased. GLM analysis revealed C18:1 as the only altered metabolite that showed a significant decrease in FEP patients after treatment. The post-treatment AC values for FEP patients were not significantly different from the corresponding values for CS, demonstrating that antipsychotic treatment enabled restoration of the values of ACs to the levels of CS.

Increased levels of LCACs (particularly C16 and C18:1) (Rizza *et al*. 2014) have been associated with cellular stress (McCoin *et al*. 2015a), mitochondrial alterations, or an increase in cellular inflammation (McCoin *et al*. 2015b; Aguer *et al*. 2015), while decreased levels of LCACs (particularly C14:1, C16 and C18:1) (Fastner *et al*. 2018) might indicate lower cellular inflammation processes. In general, accumulation of LCACs inhibits oxidative phosphorylation (Korge *et al*. 2003), impairs cell insulin signalling (Koves *et al*. 2008; Aguer *et al*. 2015), modulates cell membrane ion channels and increases membrane permeability. It has also been found that LCAC C18:1 at high nanomolar concentrations inhibits glycine transport via glycine transporter GlyT2 (related to the nociceptive pathways) (Carland *et al*. 2013). Inflammation and nociception are long known to be interconnected and LCACs have been hypothesized to serve as bioactive stress signals under circumstances when their accumulation is abnormally high (Adams *et al*. 2009; Koves *et al*. 2008). In addition, fasting plasma LCACs may be elevated in chronic metabolic diseases such as obesity and type 2 diabetes mellitus, although patients with diabetes may also have elevated levels of short- and medium-chain ACs (Sampey *et al.* 2012; Muoio *et al.* 2012; Aguer *et al*. 2015).

The increase in LCACs in the FEP patients may indicate the presence of systemic low-grade inflammation, as the ratio of LCAC to CARN (CPT-1) was significantly shifted toward the formation of LCACs. By contrast, the ratio of SCACs to CARN showed reduced formation of C3 and C5 in FEP patients at baseline. The ratio of C3 and C5 to CARN, as well as BMI were elevated after continuous treatment with antipsychotic drugs for seven months. This finding seems to emphasize the role of SCACs in the regulation of energy metabolism as higher circulating concentrations of SCACs (especially C3 and C5-DC) have been associated with the development of type 2 diabetes (Newgard *et al*. 2009). Based on existing data, FEP patients have been shown to display some signs of pre-diabetes and glucose dysregulation (Foley & Morley, 2011; Henderson *et al*. 2015; Perry *et al*. 2016; Garcia-Rizo *et al*. 2017). Emerging domination of LCACs, mitochondrial overload and incomplete FAO start to affect insulin sensitivity. Due to the amphipathic nature of LCACs (C16, C18), they can reside in cell membranes and interfere with insulin signalling directly from the membrane. Changes in glucose metabolism are especially important in developing the risk of metabolic syndrome or type 2 diabetes. Often this can be

associated to the side effects of antipsychotic treatment, however SCZ was already found to be associated with higher rates of diabetes before the neuroleptic era (Kohen 2004) and a recent meta-analysis by Pillinger *et al*. (2017) has supported the understanding that alterations in glucose levels are part of the disease present from its onset. Another piece of evidence supports the fact that FEP is accompanied by disturbances in glucose utilization and energy production (Holmes *et al*. 2006; Greenhalgh *et al.* 2017).

The current data from the FEP patients compared to CS also demonstrated an increase in hexose level which indicates potential changes in carbohydrate metabolism (Paper I). All these above-mentioned shifts (SCACs, LCACs, hexose) may evidence certain MitoDys, as the metabolism pathways of lipids, glucose and amino acids cross in the mitochondria.

6.2. Selected inflammatory biomarkers in first-episode psychosis before and after seven-month antipsychotic treatment (Paper II)

Activation of the inflammatory response system in SCZ has been noted and evidenced for decades and several authors have studied these findings in detail (Fan *et al*. 2007; Potvin *et al*. 2008; Müller and Schwarz, 2010; Drexhage *et al*. 2010). Inflammatory changes have been found to be present in subjects with drug-naïve FEP compared to controls, suggesting that shifts in the levels of inflammatory biomarkers are independent of the effects of antipsychotic medications (Kirkpatrick & Miller 2013). Our current inflammatory profiling also supports the notion that the levels of several inflammatory biomarkers in antipsychotic-naïve FEP patients compared to CS are changed: the levels of ferritin (an acute phase protein), PAI-1 (being an important regulator of fibrinolysis), and IL-6 (a pro-inflammatory CK involved predominantly in inflammation through monocytes/macrophages and also regulating metabolic processes) showed a statistically significant increase in antipsychotic-naïve FEP patients. Elevation of the above-mentioned markers indicates possible signs of low-grade inflammatory processes in FEP, which is in accordance with other studies that have reported the elevation of IL-6 (Song *et al*. 2013; Di Nicola *et al*. 2013; Stojanovic *et al*. 2014; Upthegrove *et al*. 2014; Petrikis *et al.* 2015; Bocchio-Chiavetto *et al*. 2018), as well as ferritin and PAI-1 (Hoirisch-Clapauch *et al*. 2016; Schwarz *et al*. 2010; Bocchio-Chiavetto *et al*. 2018) in FEP patients. Data from the literature confirm that pro-inflammatory CKs, such as IL-6 but also IL-1β and TNF-α, play an essential role in the modulation of various cerebral functions (Larson and Dunn 2001; Anisman *et al*. 2002) and enhanced peripheral and/or central pro-inflammatory CK signalling has notably been shown to impair affective, emotional and social functions (Dantzer *et al*. 2008). Animal models have revealed that peripheral and/or central administration of pro-inflammatory CK-releasing agents markedly induces anhedonic behaviour and social impairments (Anisman *et al*. 2002; Dantzer *et al*. 2008),

both of which have been associated with the negative symptoms of SCZ (Möller 2007; Tandon *et al*. 2009). Furthermore, enhanced release of IL-6 as a result of peripheral inflammation has been associated with two other distinctive features of negative symptoms: deficiency in sustained attention (Holden *et al*. 2008) and psychomotor retardation (Brydon *et al*. 2008).

There is evidence that antipsychotic drugs can modulate components of the inflammatory-related pathways (Meyer *et al*. 2008) and can also reduce the emerging signs of metabolic syndrome (Haring *et al*. 2015; Miller *et al*. 2011; Upthegrove *et al*. 2014). In addition, CKs have been found to regulate immune/ inflammatory reactions and brain development, and to influence the dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission (Miller *et al*. 2011; Watanabe *et al*. 2010; Müller *et al*. 2015). The results of our study on the FEP patient population indicated that 7-month antipsychotic treatment had an effect on several inflammatory biomarkers, but the strongest decline occurred in the level of ferritin, followed by IL-1α (Paper II). Antipsychotic treatment was also associated with a decrease in IL-6 as well as in PAI-1 levels, both of which demonstrated a medium-size effect, however considering the small group of the study patients, these results lost their validity after the Bonferroni correction for multiple comparisons. When comparing the effects of antipsychotic treatment in FEP patients to the biomarker levels in CS, the most prominent difference was seen in IL-1α levels, which fell below the corresponding levels in CS and demonstrated a medium-size effect. The levels of the other inflammatory biomarkers (ferritin, TNF-α and PAI-1 and IL-6) returned to the corresponding levels in CS. Although there is no final consensus on the state and trait makers of FEP and SCZ, it is evident that the peripheral immune system is over-activated in individuals undergoing their FEP and also in people suffering from chronic SCZ (Lai *et al*. 2016).

Antipsychotic treatment causes significant reduction in the psychopathology (PANSS) total score, while its negative and obvious impact was an increase in BMI (a common side-effect of antipsychotic medication) (Bak *et al*. 2014; De Hert *et al*. 2009; McEvoy *et al*. 2005). This is consistent with the results of the present study, as the BMI values did not differ between antipsychotic-naïve FEP patients and CS at baseline, but the increase after the 7-month antipsychotic treatment was significant. There can be several reasons for such BMI increase. Firstly, it is a known side-effect of antipsychotic drugs (such as olanzapine and clozapine) (Bak *et al*. 2014; De Hert *et al*. 2009); secondly, it might be caused by changes in the surrounding environment of the patients, including everyday care. The effect of limited physical activity of patients cannot be neglected (De Hert *et al*. 2009; Rastad *et al*. 2014). These results are in accordance with a meta-analysis by Tarricone *et al*. (2010), which enrolled antipsychotic-naïve patients and reported an increase in BMI immediately after the first exposure to antipsychotics, particularly during the first two months, which continued to increase up to a year or more of treatment. In addition, Bak *et al*. (2014) reported that weight gain continues over time and is associated with prolonged antipsychotic use.

6.3. Oxidative stress markers in first-episode psychosis before and after seven-month antipsychotic treatment (Paper III)

One of the mechanisms of the etiology of SCZ is the faulty antioxidant system, which results in increased lipid peroxides, causing membrane defects, immune system dysfunction and pathology of different systems of neurotransmitters in SCZ (Yao and Keshavan 2011). Along with abnormal inflammation, OxS is another pathogenic process that contributes to the poor outcome of SCZ (Bošković *et al*. 2011; Mitra *et al.* 2017). Elevation of plasma lipid peroxides has been shown to be present at the onset of psychosis in never-medicated, first-episode SCZ patients (Mahadik *et al.* 1998). This suggests the presence of OxS already very early in the course of the illness, irrespective of treatment. In addition to peripheral OxS, increased neuronal OxS levels affect signal transduction, structural plasticity and cellular resilience, mostly by inducing lipid peroxidation in membranes and direct damage to protein and genes (Gama *et al*. 2007; Gama *et al*. 2008a; Gama *et al*. 2008b). Neurons and glia cells are particularly vulnerable to inflammatory processes and changes in the redox status and are dependent on maintaining neurotrophic activity (Kapczinski *et al*. 2010; Kapczinski *et al*. 2011; Kunz *et al*. 2008; Kunz *et al*. 2011). Furthermore, oxidative stress has been identified as a possible element in the neuropathological processes of SCZ (Riegel *et al*. 2010; Dietrich-Muszalska & Kontek, 2010; Kunz *et al*. 2008; Gama *et al*. 2008a; Gama *et al*. 2008b).

In our OxS study of peripheral biomarkers, we failed to reveal significant differences in OxS-related parameters such as TPX, TAC, OSI and Met-SO/Met, when comparing FEP patients to CS. In other words, total antioxidative capacity, lipid peroxidation and protein-oxidation related indices did not differ in FEP patients before treatment compared to CS. These results are consistent with a study performed on FEP patients by Noto *et al*. 2015. According to multivariate GLM analysis for the potential effect of FEP on the combination of OxS markers, the main effect of the disease resulted in slightly increased OSI level. Studies by other groups have shown associations between FEP and increased status of OxS (Martínez-Cengotitabengoa *et al*. 2012; Fournier *et al*. 2014; Sarandol *et al*. 2015). Although the nature of OxS, whether lipid-related or protein-related, and the grade of OxS (low-grade, high-grade) in FEP remain elusive, the data of this thesis indicate that FEP could be described as an increase in OSI level; also, at the whole model level there was a moderate effect on OxS markers.

In our study, seven-month antipsychotic treatment in FEP patients caused a significant decrease in TPX and OSI compared to the baseline status of the FEP group. Although there were no changes in lipid-related OxS, the treatment caused a favourable decrease in protein-related OxS by lowering the levels of Met-SO and Met-SO/Met and increasing the level of Met. After using repeated measures GLM to assess the main effects of the 7-month antipsychotic

treatment on serum biomarker levels, with all OxS markers taken into account, a decrease was detected in serum TPX and OSI; the levels of the other markers being similar for pre- and post-treatment timepoints. When comparing the FEP patients after treatment with CS, there was a significant increase in Met and a decrease in Met-SO and Met-SO/Met; the levels of TAC, TPX and OSI were comparable for both groups.

As a result of 7-month antipsychotic treatment, there was a decrease in OxS status. In addition to reduced lipid peroxidation and protein oxidation related indices of OxS, this study also highlights improvement in the inflammatory status with antipsychotic treatment. Therefore, the treatment strategy in FEP patients needs to consider both inflammation and OxS as closely interrelated counterparts for the following reasons. Firstly, there exist correlations between inflammatory and OxS markers in FEP patients, as inflammation is associated with elevated levels of reactive oxygen species. Secondly, antipsychotic treatment significantly improves inflammatory signature in FEP patients and has a positive impact on the indices of OxS at the early stage of this psychotic disorder because anti-inflammatory cascades are related to reduced ROS concentrations. In addition, recent reviews and meta-analyses (Bitanihirwe & Woo 2011; Flatow *et al*. 2013; Leza *et al*. 2015), studying the interactions between inflammation and OxS, highlight their close relationship in SCZ and emphasize that these two may be both the causes and consequences of cellular pathology.

It is appropriate to underline that the profiling of ACs also showed modifications in the LCACs profile, which can reflect severity of inflammation. It should be noted that the seven-month treatment with antipsychotics not only normalizes inflammatory and OxS responses but also restores the profile of LCACs.

6.4. Specific biomarkers for first-episode psychosis before and after antipsychotic treatment

Our studies in FEP patients confirm the shifts in the levels of different biomarkers that were already present before the start of antipsychotic treatment (Papers I–III, Figure 4). The increase in LCACs (C14:1, C16, C16:1, C18:1) can indicate mitochondrial dysfunction, cellular stress or cellular inflammation. This assumption is supported by the fact that FEP patients also demonstrated increased levels of the non-specific acute-phase inflammatory marker ferritin, pro-inflammatory CK IL-6 and PAI-1. The elevated levels of PAI-1 have been found to be present in metabolic syndrome (Hoirisch-Clapauch *et al*. 2016; Jung *et al*. 2018; Bocchio-Chiavetto *et al*. 2018). The ratio of SCACs to CARN showed reduced formation of C3 and C5 in antipsychotic-naïve FEP patients, whereas the formation of LCACs prevailed. Increased levels of LCACs have been found to inhibit energy metabolism and impair insulin signalling of the

cells (Koves *et al*. 2008; Muoio *et al*. 2012; Noland *et al*. 2009; Adams *et al*. 2009; Sampey *et al*. 2012).

Seven-month antipsychotic treatment had several favourable impacts on the levels of metabolic, inflammatory and OxS biomarkers. Shifts in LCACs and SCACs as well as the levels of selected inflammatory biomarkers were reversed and returned to the corresponding levels in CS. Treatment also increased the level of SCAC and caused an elevation in the ratio of C3 and C5 to CARN. The status of low-grade inflammation also improved as evidenced by a marked decline in ferritin and IL-1α levels. The decline in the latter dropped lower than IL-1α level in CS. OxS markers also showed reduced indices of lipid peroxidation and protein oxidation. In general, antipsychotic treatment appears to have a positive impact on low-grade inflammation and OxS, in addition to a significant amelioration in psychotic symptoms. On the other hand, chronic exposure to antipsychotic treatment may have an impact on glucose dysregulation as elevation in C3 and C5-DC levels has been associated with the development of type 2 diabetes mellitus (Newgard *et al*. 2009).

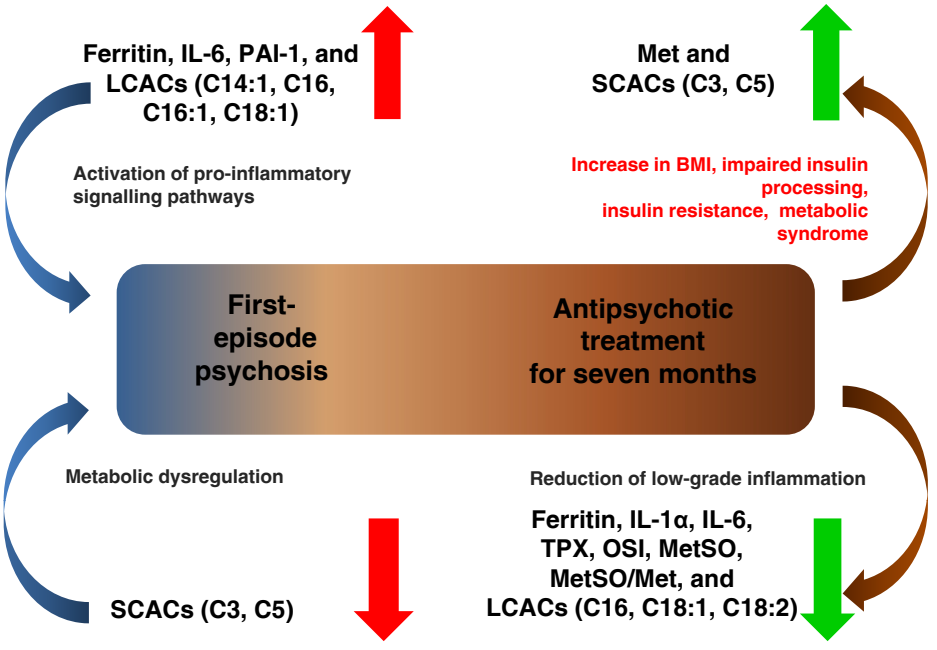

Figure 4. Changes in biomarkers due to FEP before and after seven-month antipsychotic treatment, summarizing the current results presented in this thesis. FEP: first-episode psychosis; LCACs: long-chain acylcarnitines (C14:1, C16, C16:1, C18:1, C18:2); SCACs: short-chain acylcarnitines (C3, C5); TPX: total level of peroxides; OSI: oxidative stress index; Met: methionine; Met-SO: methionine sulfoxide; Met-SO/Met: ratio of oxidized methionine to methionine; IL-1α, IL-6: interleukins; PAI-1: plasminogen activator inhibitor-1; BMI: body mass index.

Chronic treatment with antipsychotics seems to lead to pre-diabetic state. There was also a significant increase in BMI compared to its baseline levels in the patients. This has been associated with the side effects of antipsychotic drugs, but it can also be related to the sedentary lifestyle of SCZ patients compared to the general population (De Hert *et al*. 2009; Rastad *et al*. 2014). In conclusion, treatment of FEP is associated with metabolic changes and future therapies should concentrate on solutions that can avoid or minimize unwanted changes in FEP patients.

CONCLUSIONS

The results of this thesis enable to state the following:

1. The serum levels of LCACs (C14:1, C16, C16:1 and C18:1) were elevated and the level of SCAC (C3) was decreased in FEP patients compared to CS. Antipsychotic treatment returned the shifts in ACs to the corresponding level in CS, with the most marked decline seen in C18:1, and also reversed the decline in SCACs (C3 and C5) levels. The balance in the formation of SCACs (C3, C5) and LCACs via CARN was shifted to the formation of LCACs, which probably indicates low-grade inflammation in FEP patients. At the same time, antipsychotic treatment also decreased the level of inflammation.
2. Antipsychotic-naïve FEP patients had elevated serum levels of ferritin, PAI-1 and IL-6 compared to CS. As a result of seven-month antipsychotic treatment, the most prominent decline was seen in ferritin level, followed by the decrease in IL-1α in FEP patients. Compared to CS, the decline in IL-1α exceeded the level of CS. The levels of ferritin, TNF-α, PAI-1 and IL-6 returned to the corresponding levels in CS as a result of antipsychotic treatment, while the obtained data also support the fact that FEP is associated with low-grade inflammation and treatment (7 months) has a positive impact by reducing inflammation.
3. Antipsychotic-naïve FEP patients did not show any significant differences in OxS-related parameters such as TPX, TAC, OSI and Met-SO/Met when compared to CS. In the FEP patient group, seven-month treatment with antipsychotics reduced the rates of protein and lipid oxidation, decreased the levels of TPX and OSI, and demonstrated also a significant increase in Met and a decrease in Met-SO and Met-SO/Met levels. Compared to CS, there were no statistically significant differences in the levels of TAC, TPX and OSI in FEP patients after treatment. Although the baseline results did not demonstrate a significant increase in OxS levels in FEP patients compared to CS, antipsychotic treatment had a positive effect by shifting the OxS levels below the values seen in controls.
4. Figure 4 shows the detailed signature of FEP in view of the change in low-grade inflammation, lipidomics (the referred ACs) and OxS status before and after seven-month treatment. As a result of seven-month antipsychotic treatment, the biomarker profile of FEP patients did not differ from that of the controls. Nevertheless, the enhanced formation of SCACs, supported by the increase in BMI, triggered impaired insulin processing, insulin resistance and metabolic syndrome, causing undesirable metabolic shifts at an early stage of the disease. Consequently, our comprehensive study of FEP highlights the efficiency of treatment at the molecular level, but also indicates that future treatment strategies should be improved to minimize the risk for the development of diabetes and metabolic syndrome.

REFERENCES

Adams SH, Hoppel CL, Lok KH, Zhao L, Wong SW, Minkler PE, Hwang DH, Newman JW, Garvey WT. 2009. "Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid beta-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic African-American women." *J Nutr.* 139 (6): 1073–81. doi:10.3945/jn.108.103754.

Aguer C, McCoin CS, Knotts TA, Thrush AB, Ono-Moore K, McPherson R, Dent R, Hwang DH, Adams SH, Harper ME. 2015. "Acylcarnitines: potential implications for skeletal muscle insulin resistance." *Faseb J.* 29 (1): 336–45. doi:10.1096/fj.14-255901.

Akiyama, K. 1999. "Serum levels of soluble IL-2 receptor alpha, IL-6 and IL-1 receptor antagonist in schizophrenia before and during neuroleptic administration." *Schizophr. Res.* 37 (1): 97–106.

Altamura AC, Pozzoli S, Fiorentini A, Dell'osso B. 2013. "Neurodevelopment and inflammatory patterns in schizophrenia in relation to pathophysiology." *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 42: 63–70. doi:10.1016/j.pnpbp.2012.08.015.

Amminger GP, Henry LP, Harrigan SM, Harris MG, Alvarez-Jimenez M, Herrman H, Jackson HJ, McGorry PD. 2011. "Outcome in early-onset schizophrenia revisited: findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study." *Schizophrenia Res.* 131 (1–3): 112–9. doi:10.1016/j.schres.2011.06.009.

Anisman H, Kokkinidis L, Merali Z. 2002. "Further evidence for the depressive effects of cytokines: anhedonia and neurochemical changes." *Brain Behav Immun.* 16 (5): 544–56.

Baganz NL, Blakely RD. 2013. "A dialogue between the immune system and brain, spoken in the language of serotonin." *ACS Chem. Neurosci.* 16;4 (1): 48–63. doi:10.1021/cn300186b.

Bak M, Fransen A, Janssen J, van Os J, Drukker M. 2014. "Almost all antipsychotics result in weight gain: a meta-analysis." *PLoS One.* 9 (4): e94112. doi:10.1371/journal.pone.0094112.

Ballageer T, Malla A, Manchanda R, Takhar J, Haricharan R. 2005. "Is adolescent-onset first-episode psychosis different from adult onset?" *J Am Acad Child Adolesc Psychiatry* 44 (8): 782–9.

Ben-Shachar, D. 2002. "Mitochondrial dysfunction in schizophrenia: a possible linkage to dopamine." *J.Neurochem.* 83: 1241–51.

Bitanihirwe BK, Woo T-UW. 2011. "Oxidative stress in schizophrenia: an integrated approach." *Neurosci Biobehav Rev.* 35 (3): 878–93. doi:10.1016/j.neubiorev.2010.10.008.

Bobo WV, Bonaccorso S, Jayathilake K, Meltzer HY. 2011. "Prediction of long-term metabolic effects of olanzapine and risperidone treatment from baseline body mass index in schizophrenia and bipolar disorder." *Psychiatry Res.* 189 (2): 200–7. doi:10.1016/j.psychres.2011.07.008.

Bocchio-Chiavetto L, Zanardini R, Tosato S, Ventriglia M, Ferrari C, Bonetto C, Lasalvia A, Giubilini F, Fioritti A, Pileggi F, Pratelli M, Pavanati M, Favaro A, De Girolamo G, Frisoni GB, Ruggeri M, Gennarelli M. 2018. "Immune and metabolic alterations in first episode psychosis (FEP) patients." *Brain Behav Immun.* 70: 315–324. doi:10.1016/j.bbi.2018.03.013.

Borovcanin M, Jovanovic I, Radosavljevic G, Djukic Dejanovic S, Stefanovic V, Arsenijevic N, Lukic ML. 2013. "Antipsychotics can modulate the cytokine profile in schizophrenia: attenuation of the type-2 inflammatory response." *Schizophr Res.* 147 (1): 103–109. doi:10.1016/j.schres.2013.03.027.

Borovcanin MM, Jovanovic I, Radosavljevic G, Pantic J, Minic Janicijevic S, Arsenijevic N, Lukic ML. 2017. "Interleukin-6 in Schizophrenia-Is There a Therapeutic Relevance?" *Front Psychiatry.* 8: 221. doi:10.3389/fpsyt.2017.00221.

Bošković M, Vovk T, Kores Plesničar B, Grabnar I. 2011. "Oxidative stress in schizophrenia." *Curr Neuropharmacol.* 9 (2): 301–12. doi:10.2174/157015911795596595.

Breitborde NJK, Srihari VH, Woods SW. 2009. "Review of the operational definition for first-episode psychosis." *Early Interv Psychiatry* 3 (4): 259–65. doi:10.1111/j.1751-7893.2009.00148.x.

Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. 2008. "Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans." *Biol Psychiatry.* 63 (11): 1022–9. doi:10.1016/j.biopsych.2007.12.007.

Cai J, Jones DP. 1998. "Superoxide in apoptosis. Mitochondrial generation triggered by cytochrome c loss." *J Biol Chem.* 273 (19): 11401–4.

Carland JE, Mansfield RE, Ryan RM, Vandenberg RJ. 2013. "Oleoyl-L-carnitine inhibits glycine transport by GlyT2." *Br J Pharmacol.* 168 (4): 891–902. doi:10.1111/j.1476-5381.2012.02213.x.

Carlsson, A. 1988. "The current status of the dopamine hypothesis of schizophrenia." *Neuropsychopharmacology* 1 (3): 179–86.

Chase KA, Cone JJ, Rosen C, Sharma RP. 2016. "The value of interleukin 6 as a peripheral diagnostic marker in schizophrenia." *BMC Psychiatry* 16: 152. doi:10.1186/s12888-016-0866-x.

Chou DB, Sworder B, Bouladoux N, Roy CN, Uchida AM, Grigg M, Robey PG, Belkaid Y. 2012. "Stromal-derived IL-6 alters the balance of myeloerythroid progeni-tors during Toxoplasma gondii infection." *J Leukoc Biol.* 92 (1): 123–31. doi:10.1189/jlb.1011527.

Cohen, J. 1988. *Statistical Power Analysis for the Behaviour Sciences.* Edited by Lawrence Erlbaum. Vol. 2nd ed. Hillsdale, NJ.

Coleman RA, Lewin TM, Van Horn CG, Gonzalez-Baró MR. 2002. "Do long-chain acyl-CoA synthetases regulate fatty acid entry into synthetic versus degradative pathways?" *J Nutr.* 132 (8): 2123–6.

Conus, P, Ward, J, Lucas, N, Cotton, S, Yung, AR, Berk, M, McGorry, PD. 2010. "Characterisation of the prodrome to a first episode of psychotic mania: results of a retrospective study." *J Affect Disord* 124 (3): 341–5. doi:10.1016/j.jad.2009.12.021.

Crespo-Facorro B, Pérez-Iglesias R, Mata I, et al. 2012. "Longterm (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis." *Psychopharmacology (Berl).* 219: 225–33.

Curfs JH, Meis J.F, Hoogkamp-Korstanje JA. 1997. "A primer on cytokines: sources, receptors, effects, and inducers." *Clin. Microbiol. Rev.* 10 (4): 742–80.

D, Kohen. 2004. "Diabetes mellitus and schizophrenia: Historical perspective. ." *Br J Psychiatry Suppl* 47: S64–S6.

Dadheech G, Mishra S, Gautam S, Sharma P. 2008. “Evaluation of antioxidant deficit in schizophrenia.” *Indian J Psychiatry.* 50 (1): 16–20. doi:10.4103/0019-5545.39753.

Dakhale G, Khanzode S, Khanzode S, Saoji A, Khobragade L, Turankar A. 2004. “Oxidative damage and schizophrenia: the potential benefit by atypical antipsychotics.” *Neuropsychobiology.* 49 (4): 205–9. doi:10.1159/000077368.

Dantzer R, O’Connor JC, Freund GG, Johnson RW, Kelley KW. 2008. “From inflammation to sickness and depression: when the immune system subjugates the brain.” *Nat Rev Neurosci.* 9 (1): 46–56. doi:10.1038/nrn2297.

Davies G, Haddock G, Yung AR, Mulligan LD, Kyle SD. 2017. “A systematic review of the nature and correlates of sleep disturbance in early psychosis.” *Sleep Med Rev.* 31: 25–38. doi:10.1016/j.smrv.2016.01.001.

Davis, KL, Kahn, RS, Ko, G, Davidson, M. 1991. “Dopamine in schizophrenia: a review and reconceptualization.” *Am J Psychiatry* 148 (11): 1474–1486.

De Hert M, Schreurs V, Vancampfort D, Van Winkel R. 2009. “Metabolic syndrome in people with schizophrenia: a review.” *World Psychiatry.* 8 (1): 15–22.

de Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS, Bahn S. 2014. “Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment.” *Schizophr Res.* 154 (1–3): 23–9. doi:10.1016/j.schres.2014.02.005.

Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, Murray RM, Dazzan P, Pariante CM, Mondelli V. 2013. “Serum and gene expression profile of cytokines in first-episode psychosis.” *Brain Behav Immun.* 31: 90–5. doi:10.1016/j.bbi.2012.06.010.

Diaz-Caneja CM, Pina-Camacho L, Rodriguez-Quiroga A, Fraguas D, Parellada M, Arango C. 2015. “Predictors of outcome in early-onset psychosis: a systematic review.” *NPJ Schizophr.* 4;1:14005. doi:10.1038/npjschz.2014.5.

Dickinson D, Ragland JD, Gold JM, & Gur RC. 2008. “General and specific cognitive deficits in schizophrenia: Goliath defeats David?” *Biological psychiatry* 64: 823–827.

Dietrich-Muszalska A, Kontek B. 2010. “Lipid peroxidation in patients with schizophrenia.” *Psychiatry Clin Neurosci.* 64 (5): 469–75. doi:10.1111/j.1440-1819.2010.02132.x.

Dinarello, CA. 2000. “Proinflammatory cytokines.” *Chest.* 118 (2): 503–8.

Ding M, Song X, Zhao J, Gao J, Li X, Yang G, Wang X, Harrington A, Fan X, Lv L. 2014. “Activation of Th17 cells in drug naïve, first episode schizophrenia.” *Prog Neuropsychopharmacol Biol Psychiatry.* 51: 78–82. doi:10.1016/j.pnpbp.2014.01.001.

Do KQ, Cabungcal JH, Frank A, Steullet P, and Cuenod M. 2009. “Redox dysregulation, neurodevelopment, and schizophrenia.” *Curr Opin Neurobiol.* 19 (2): 220–30. doi:10.1016/j.conb.2009.05.001.

Drexhage RC, van der Heul-Nieuwenhuijsen L, Padmos RC, van Beveren N, Cohen D, Versnel MA, Nolen WA, Drexhage HA. 2010 . “Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients.” *Int J Neuropsychopharmacol.* 13 (10): 1369–81. doi:10.1017/S1461145710000799.

D’Souza K, Nzirorera C, Kienesberger PC. 2016. “Lipid metabolism and signaling in cardiac lipotoxicity.” *Biochim Biophys Acta.* 1861 (10): 1513–24. doi:10.1016/j.bbalip.2016.02.016.

Emsley R, Chiliza B, Asmal L, Harvey BH. 2013. “The nature of relapse in schizophrenia.” *BMC Psychiatry.* 8;13:50. doi:10.1186/1471-244X-13-50.

Evans MD, Cooke MS. 2004. “Factors contributing to the outcome of oxidative damage to nucleic acids.” *Bioessays.* 26 (5): 533–42.

Fan X, Goff DC, Henderson DC. 2007. “Inflammation and schizophrenia.” *Expert Rev Neurother* 7 (7): 789–96.

Fastner C, Behnes M, Sartorius B, Wenke A, Lang S, Yücel G, Sattler K, Rusnak J, Saleh A, Barth C, Mashayekhi K, Hoffmann U, Borggrefe M, Akin I. 2018. “Interventional Left Atrial Appendage Closure Affects the Metabolism of Acylcarnitines.” *Int J Mol Sci.* 19 (2): E500. doi:10.3390/ijms19020500.

Felger JC, Miller AH. 2012. “Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise.” *Front. Neuroendocrinol.* 33 (3): 315–27. doi:10.1016/j.yfrne.2012.09.003.

Fernandez-Egea E, Bernardo M, Donner T, Conget I, Parellada E, Justicia A, Esmatjes E, Garcia-Rizo C, Kirkpatrick B. 2009. “Metabolic profile of antipsychotic naive individuals with non-affective psychosis.” *Br J Psychiatry* 194 (5): 434–8. doi:10.1192/bjp.bp.108.052605.

Fiehn O, Garvey WT, Newman JW, Lok KH, Hoppel CL, Adams SH. 2010. “Plasma metabolomic profiles reflective of glucose homeostasis in non-diabetic and type 2 diabetic obese African-American women.” *PLoS One* 5 (12): e15234. doi:10.1371/journal.pone.0015234.

Flatow J, Buckley P, Miller BJ. 2013. “Meta-analysis of oxidative stress in schizophrenia.” *Biol Psychiatry.* 74 (6): 400–9. doi:10.1016/j.biopsych.2013.03.018.

Foley DL, Morley KI. 2011. “Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis.” *Arch Gen Psychiatry.* 68 (6): 609–16. doi:10.1001/archgenpsychiatry.2011.2.

Fond G, d’Albis MA, Jamain S, Tamouza R, Arango C, Fleischhacker WW, Glenthøj B, Leweke M, Lewis S, McGuire P, Meyer-Lindenberg A, Sommer IE, Winter-van Rossum I, Kapur S, Kahn RS, Rujescu D, Leboyer M. 2015. “The promise of biological markers for treatment response in first-episode psychosis: a systematic review.” *Schizophr Bull.* 41 (3): 559–73. doi:10.1093/schbul/sbv002.

Fonseka TM, Müller DJ, Kennedy SH. 2016. “Inflammatory Cytokines and Antipsychotic-Induced Weight Gain: Review and Clinical Implications.” *Mol Neuropsychiatry.* 2 (1): 1–14. doi:10.1159/000441521.

Fournier M, Ferrari C, Baumann PS, Polari A, Monin A, Bellier-Teichmann T, Wulff J, Pappan KL, Cuenod M, Conus P, Do KQ. 2014. “Impaired metabolic reactivity to oxidative stress in early psychosis patients.” *Schizophr Bull.* 40 (5): 973–83. doi:10.1093/schbul/sbu053.

Fraguas D, Díaz-Caneja CM, Rodríguez-Quiroga A, Arango C. 2017. “Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis.” *Int J Neuropsychopharmacol.* 20 (6): 435–44. doi:10.1093/ijnp/pyx015.

Fusar-Poli P, Yung AR, McGorry P, van Os J. 2014. “Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention.” *Psychol Med.* 44 (1): 17–24. doi:10.1017/S0033291713000184.

Gallin JI, Snyderman R, Fearon DT, Haynes BF, Nathan C. 1999. *Inflammation: Basic Principles and Clinical Correlates.* Philadelphia: Lippincott Williams & Wilkins.

Gama CS, Andreazza AC, Kunz M, Berk M, Belmonte-de-Abreu PS, Kapczinski F. 2007. “Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder.” *Neurosci Lett.* 420 (1): 45–8. doi:10.1016/j.neulet.2007.04.001.

Gama CS, Berk M, Andreazza AC, Kapczinski F, Belmonte-de-Abreu P. 2008a. “Serum levels of brain-derived neurotrophic factor and thiobarbituric acid reactive substances in chronically medicated schizophrenic patients: a positive correlation.” *Revista* 30 (4): 337–40.

Gama CS, Salvador M, Andreazza AC, Lobato MI, Berk M, Kapczinski F, Belmonte-de-Abreu PS. 2008b. “Elevated serum thiobarbituric acid reactive substances in clinically symptomatic schizophrenic males.” *Neurosci Lett.* 433 (3): 270–3. doi:10.1016/j.neulet.2008.01.018.

Garcia-Rizo C, Fernandez-Egea E, Oliveira C, Meseguer A, Cabrera B, Mezquida G, Bioque M, Penades R, Parellada E, Bernardo M, Kirkpatrick B. 2017. “Metabolic syndrome or glucose challenge in first episode of psychosis?” *Eur Psychiatry.* 41: 42–46. doi:10.1016/j.eurpsy.2016.10.001.

Gardner DM, Murphy AL, O’Donnell H, Centorrino F, Baldessarini RJ. 2010. “International consensus study of antipsychotic dosing.” *Am. J. Psychiatry* 167: 686−93.

Gee DG, Cannon TD. 2011. “Prediction of conversion to psychosis: review and future directions.” *Rev Bras Psiquiatr.* 33 Suppl 2: 129–42.

Girgis RR, Kumar SS, Brown AS. 2014. “The cytokine model of schizophrenia: emerging therapeutic strategies.” *Biol Psychiatry* 75 (4): 292–299.

Gladkevich A, Kauffman HF, Korf J. 2004. “Lymphocytes as a neural probe: Potential for studying psychiatric disorders.” *Prog Neuropsychopharmacol Biol Psychiatry.* 28 (3): 559 –76.

Greenhalgh AM, Gonzalez-Blanco L, Garcia-Rizo C, Fernandez-Egea E, Miller B, Arroyo,MB, Kirkpatrick B. 2017. “Metaanalysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with nonaffective psychosis.” *Schizophr Res.* 179: 57–63.

Guest PC, Schwarz E, Krishnamurthy D, Harris LW, Leweke FM, Rothermundt M, van Beveren NJ, Spain M, Barnes A, Steiner J, Rahmoune H, Bahn S. 2011. “Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia.” *Psychoneuroendocrinology* 36 (7): 1092–6. doi:10.1016/j.psyneuen.2010.12.018.

Guest PC, Wang L, Harris LW, Burling K, Levin Y, Ernst A, Wayland MT, Umrania Y, Herberth M, Koethe D, van Beveren JM, Rothermundt M, McAllister G, Leweke FM, Steiner J, Bahn S. 2010. “Increased levels of circulating insulin-related peptides in first-onset, antipsychotic naive schizophrenia patients.” *Mol Psychiatry* 15 (2): 118–9. doi:10.1038/mp.2009.81.

Halliwell, B. 1996. “Antioxidants in human health and disease.” *Annu Rev Nutr.* 16: 33–50. doi:10.1146/annurev.nu.16.070196.000341.

Halliwell, B. 2006a. “Oxidative stress and neurodegeneration: where are we now?” *J. Neurochem.* 97 (6): 1634–58. doi:10.1111/j.1471-4159.2006.03907.x.

Halliwell, B. 2006b. “Reactive species and antioxidants: redox biology is a fundamental theme of aerobic life.” *Plant Physiol.* 141 (2): 312–22. doi:10.1104/pp.106.077073.

Haring L, Koido K, Vasar V, Leping V, Zilmer K, Zilmer M, Vasar E. 2015. “Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first-episode psychosis patients, but increases their body mass index.” *Schizophr Res.* 169 (1–3): 22–9. doi:10.1016/j.schres.2015.08.027.

Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. 2015. "Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses." *Lancet Psychiatry.* 2 (5): 452–64. doi:10.1016/S2215-0366(15)00115-7.

Ho JK, Duclos RI Jr, Hamilton JA. 2002. "Interactions of acyl carnitines with model membranes: a (13)C-NMR study." *J Lipid Res.* 43 (9): 1429–39.

Hoirisch-Clapauch S, Amaral OB, Mezzasalma MA, Panizzutti R, Nardi AE. 2016 . "Dysfunction in the coagulation system and schizophrenia." *Transl Psychiatry.* 6: e704. doi:10.1038/tp.2015.204.

Holden JM, Meyers-Manor JE, Overmier JB, Gahtan E, Sweeney W, Miller H. 2008. "Lipopolysaccharide-induced immune activation impairs attention but has little effect on short-term working memory." *Behav Brain Res.* 194 (2): 138–45. doi:10.1016/j.bbr.2008.06.032.

Holland WL, Knotts TA, Chavez JA, Wang LP, Hoehn KL, Summers SA. 2007. "Lipid mediators of insulin resistance." *Nutr Rev.* 65 (6): 39–46.

Holmes E, Tsang TM, Huang JT, Leweke FM, Koethe D, Gerth CW, Nolden BM, Gross S, Schreiber D, Nicholson JK, Bahn S. 2006. "Metabolic profiling of CSF: evidence that early intervention may impact on disease progression and outcome in schizophrenia." *PLoS Med.* 3 (8): e327. doi:10.1371/journal.pmed.0030327.

Horrobin, DF. 1998. "The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia." *Schizophr Res.* 30 (3): 193–208.

Horrocks LA, Farooqui AA. 2004. "Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function." 70 (4): 361–72. doi:10.1016/j.plefa.2003.12.011.

Howes OD, Kapur S. 2014. "A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic)." *Br J Psychiatry.* 205 (1): 1–3.

Howes OD, Nour MM. 2016. "Dopamine and the aberrant salience hypothesis of schizophrenia." *World Psychiatry* 15 (1): 3–4. doi:10.1002/wps.20276.

Häfner H, Maurer K, Löffler W, Bustamante, S, van der Heiden, W, Riecher-Rössler, A, Nowotny, B. 1995. *Onset and early course of schizophrenia.* Vol. Search for the causes of schizophrenia. III vols. Berlin Heidelberg: Springer-Verlag.

IPCS, International Programme on Chemical Safety. n.d. Accessed February 2, 2018. http://www.inchem.org/documents/ehc/ehc/ehc155.htm.

Joa I, Johannessen JO, Langeveld J, Friis S, Melle I, Opjordsmoen S, Simonsen E, Vaglum P, McGlashan T, Larsen TK. 2009. "Baseline profiles of adolescent vs. adult-onset first-episode psychosis in an early detection program." *Acta Psychiatr Scand.* 119 (6): 494–500. doi:10.1111/j.1600-0447.2008.01338.x.

Jung RG, Simard T, Labinaz A, Ramirez FD, Di Santo P, Motazedian P, Rochman R, Gaudet C, Faraz MA, Beanlands RSB, Hibbert B. 2018. "Role of plasminogen activator inhibitor-1 in coronary pathophysiology." *Thromb Res.* 164: 54–62. doi:10.1016/j.thromres.2018.02.135.

Kaddurah-Daouk R, Krishnan KR. 2009. "Metabolomics: a global biochemical approach to the study of central nervous system diseases." *Neuropsychopharmacology.* 34 (1): 173–86. doi:10.1038/npp.2008.174.

Kahn, RS & Sommer, IE. 2015. "The neurobiology and treatment of first-episode schizophrenia." *Molecular Psychiatry* 20: 84–97.

Kaldur T, Kals J, Ööpik V, Zilmer M, Zilmer K, Eha J, Unt E. 2014. “Effects of heat acclimation on changes in oxidative stress and inflammation caused by endurance capacity test in the heat.” *Oxid Med Cell Longev.* 2014: 107137. doi:10.1155/2014/107137.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Moreira JC, de Bittencourt Pasquali MA, Fries GR, Quevedo J, Gama CS, Post R. 2011 . “Peripheral biomarkers and illness activity in bipolar disorder.” *J Psychiatr Res.* 45 (2): 156–61. doi:10.1016/j.jpsychires.2010.05.015.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Pasquali MA, Quevedo J, Gama CS, Post R. 2010 . “A systemic toxicity index developed to assess peripheral changes in mood episodes.” *Mol Psychiatry.* 15 (8): 784–6. doi:10.1038/mp.2009.112.

Kaur S, Zilmer K, Leping V, Zilmer M. 2012. “Comparative study of systemic inflammatory responses in psoriasis vulgaris and mild to moderate allergic contact dermatitis.” *Dermatology.* 225 (1): 54–61. doi:10.1159/000339866.

Kaur T, Cadenhead KS. 2010. “Treatment implications of the schizophrenia prodrome.” *Curr Top Behav Neurosci.* 4: 97–121.

Kay SR, Fiszbein A, Opler LA. 1987. “The positive and negative syndrome scale (PANSS) for schizophrenia.” *Schizophrenia Bulletin* 13 (2): 261–76.

Kell DB, Pretorius E. 2014. “Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells.” *Metallomics* 6: 748.

Keller WR, Fischer BA, Carpenter WT Jr. 2011. “Revisiting the diagnosis of schizophrenia: where have we been and where are we going?” *CNS Neurosci Ther* 17: 83–88.

Kim JS, Kornhuber HH, Schmid-Burgk W, Holzm€uller B. 1980. “Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis onschizophrenia.” *Neuroscience Letters* 20: 379–382.

Kim YK, Myint AM, Verkerk R, Scharpe S, Steinbusch H, Leonard B. 2009. “Cytokine changes and tryptophan metabolites in medication-naive and medication-free schizophrenic patients.” *Neuropsychobiology* 59 (2): 123–9. doi:10.1159/000213565.

Kirkpatrick B, Miller BJ. 2013. “Inflammation and schizophrenia.” *Schizophr. Bull* 39 (6): 1174–9. doi:10.1093/schbul/sbt141.

Kirkpatrick B, Miller BJ, Garcia-Rizo C, Fernandez-Egea E, Bernardo M. 2012. “Is abnormal glucose tolerance in antipsychotic-naive patients with nonaffective psychosis confounded by poor health habits?” *Schizophr Bull.* 38 (2): 280–4. doi:10.1093/schbul/sbq058.

Korge P, Honda HM, Weiss JN. 2003. “Effects of fatty acids in isolated mitochondria: implications for ischemic injury and cardioprotection.” *Am J Physiol Heart Circ Physiol.* 285 (1): H259–69. doi:10.1152/ajpheart.01028.2002.

Kouttab NM, De Simone C. 1993. “Modulation of cytokine production by carnitine.” *Mediators Inflamm.* 2 (7): 25−8.

Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, Lopaschuk GD, Muoio DM. 2008. “Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance.” *Cell Metab.* 7 (1): 45–56. doi:10.1016/j.cmet.2007.10.013.

Kronfol Z, Remick DG. 2000. “Cytokines and the brain: Implications for clinical psychiatry.” *Am J Psychiatry* 157 (5): 683– 94.

Kubistova A, Horacek J, Novak T. 2012. “Increased interleukin-6 and tumor necrosis factor alpha in first-episode schizophrenia patients versus healthy controls.” *Psychiatr Danub.* 24 Suppl 1: 153–6.

Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. 2002. “Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder.” *Cell. Biochem. Funct.* 20 (2): 171–5. doi:10.1002/cbf.940.

Kunz M, Ceresér KM, Goi PD, Fries GR, Teixeira AL, Fernandes BS, Belmonte-de-Abreu PS, Kauer-Sant’Anna M, Kapczinski F, Gama CS. 2011. “Serum levels of IL-6, IL-10 and TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance.” *Rev Bras Psiquiatr.* 33 (3): 268–74.

Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, Belmonte-de-Abreu PS, Berk M, Kapczinski F. 2008. “Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia.” *Prog Neuropsychopharmacol Biol Psychiatry.* 32 (7): 1677–81. doi:10.1016/j.pnpbp.2008.07.001.

Kurutas, EB. 2016. “The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state.” *Nutr J.* 15 (1): 71. doi:10.1186/s12937-016-0186-5.

Lai CY, Scarr E, Udawela M, Everall I, Chen WJ, Dean B. 2016. “Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics.” 22;6 (1): 102–17. doi:10.5498/wjp.v6.i1.102.

Larson SJ, Dunn AJ. 2001. “Behavioral effects of cytokines.” *Brain Behav Immun.* 4: 371–87. doi:10.1006/brbi.2001.0643.

Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. 2005. “Adipokines: molecular links between obesity and atheroslcerosis.” *Am J Physiol Heart Circ Physiol.* 288 (5): H2031–41.

Lee M, Jayathilake K, Dai J, Meltzer HY. 2011. “Decreased plasma tryptophan and tryptophan/large neutral amino acid ratio in patients with neuroleptic-resistant schizophrenia: relationship to plasma cortisol concentration.” *Psychiatry Res* 185: 328–333.

Leonard BE, Schwarz M, Myint AM. 2012. “The metabolic syndrome in schizophrenia: is inflammation a contributing cause?” *J. Psychopharmacol.* 26 (5 Suppl): 33–41. doi:10.1177/0269881111431622.

Leza JC, García-Bueno B, Bioque M, Arango C, Parellada M, Do K, O'Donnell P, Bernardo M. 2015. “Inflammation in schizophrenia: A question of balance.” *Neurosci Biobehav Rev.* 55: 612–26. doi:10.1016/j.neubiorev.2015.05.014.

Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, Pioli R, Altamura C, Scharpe S, Maes M. 1998. “The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6.” *Schizophr. Res.* 32 (1): 9–15.

Linszen D, Dingemans P, Lenior M. 2001. “Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications.” *Schizophr Res.* 51 (1): 55–61.

Liu F, Poursine-Laurent J, Wu HY, Link DC. 1997. “Interleukin-6 and the granulocyte colony stimulating factor receptor are major independent regulators of granulopoiesis in vivo but are not required for lineage commitment or terminal differentiation.” *Blood.* 90 (7): 2583–90.

Lopaschuk GD, Belke DD, Gamble J, Itoi T, Schönekess BO. 1994. “Regulation of fatty acid oxidation in the mammalian heart in health and disease.” *Biochim Biophys Acta.* 1213 (3): 263–76.

Lopresti AL, Maker GL, Hood SD, Drummond PD. 2014. “A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers.” *Prog Neuropsychopharmacol Biol Psychiatry.* 48: 102–11. doi:10.1016/j.pnpbp.2013.09.017.

MacDowell KS, García-Bueno B, Madrigal JL, Parellada M, Arango C, Micó JA, Leza JC. 2013. “Risperidone normalizes increased inflammatory parameters and resotres anti-inflammatory pathways in a model of neuroinflammation.” *Int J Neuropsychopharmacol.* 16 (1): 121–35. doi:10.1017/S1461145711001775.

Maes M, Bosmans, E, Calabrese, J, Smith, R, Meltzer, HY. 1995. “Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers.” *J. Psychiatr. Res* 29 (2): 141–152.

Mahadik SP, Evans D, Lal H. 2001. “Oxidative stress and role of antioxidant and ω-3 essential fatty acid supplementation in schizophrenia.” *Prog. Neuro-Psychopharmacol Biol. Psychiatry.* 25 (3): 463–93.

Mahadik SP, Mukherjee S, Scheffer R, Correnti EE, Mahadik JS. 1998. “Elevated plasma lipid peroxides at the onset of nonaffective psychosis.” *Biol Psychiatry.* 43 (9): 374–9.

Mahadik SP, Parikh V, and Khan MM. 2003. *The role of oxidative stress in modulating membrane and phospholipid function in schizophrenia.* Vol. Phospholipid Spectrum Disorders in Psychiatry and Neurology. Carnforth, UK: Marius Press.

Mahadik SP, Scheffer RE. 1996. “Oxidative injury and potential use of antioxidants in schizophrenia.” *Prostaglandins Leukot Essent Fatty Acids.* 55(1–2): 45–54.

Mai M, Tönjes A, Kovacs P, Stumvoll M, Fiedler GM, Leichtle AB. 2013. “Serum levels of acylcarnitines are altered in prediabetic conditions.” *PLoS One.* 8 (12): e82459. doi:10.1371/journal.pone.0082459.

Martínez-Cengotitabengoa M, Mac-Dowell KS, Leza JC, Micó JA, Fernandez M, Echevarría E, Sanjuan J, Elorza J, González-Pinto A. 2012. “Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes.” *Schizophr Res.* 137 (1–3): 66–72. doi:10.1016/j.schres.2012.03.004.

McCoin CS, Knotts TA, Adams SH. 2015b. “Acylcarnitines – old actors auditioning for new roles in metabolic physiology.” *Nat Rev Endocrinol.* 11 (10): 617–25. doi:10.1038/nrendo.2015.129.

McCoin CS, Knotts TA, Ono-Moore KD, Oort PJ, Adams SH. 2015a. “Long-chain acylcarnitines activate cell stress and myokine release in C2C12 myotubes: calcium-dependent and -independent effects.” *Am J Physiol Endocrinol Metab.* 308 (11): E990-E1000. doi:10.1152/ajpendo.00602.2014.

McEvoy J, Baillie RA, Zhu H, Buckley P, Keshavan MS, Nasrallah HA, Dougherty GG, Yao JK, Kaddurah-Daouk R. 2013. “Lipidomics reveals early metabolic changes in subjects with schizophrenia: effects of atypical antipsychotics.” *PLoS One.* 8 (7): e68717. doi:10.1371/journal.pone.0068717.

McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stroup T, Lieberman JA. 2005. “Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III.” *Schizophr Res.* 80 (1): 19–32. doi:10.1016/j.schres.2005.07.014.

McGarry JD, Mannaerts GP, Foster DW. 1977. “A possible role for malonyl-CoA in the regulation of hepatic fatty acid oxidation and ketogenesis.” *J Clin Invest.* 60 (1): 265–70.

Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, Rosenheck RA, Daumit GL, Hsiao J, Swartz MS, Stroup TS, Lieberman JA. 2008. “Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1.” *Schizophr Res* 101 (1–3): 273–86. doi:10.1016/j.schres.2007.12.487.

Michel T, Thome J, Martin D, Nara K, Zwerina S, Tatschner T, Weijers HG, Koutsilieri E. 2004. “Cu, Zn and Mn-superoxide dismutase levels in brains of patients with schizophrenic psychosis.” *J Neural Transm (Vienna).* 111 (9): 1191–201.

Mihalik SJ, Goodpaster BH, Kelley DE, Chace DH, Vockley J, Toledo FGS, DeLany JP. 2010. “Increased levels of plasma acylcarnitines in obesity and type 2 diabetes and identification of a marker of glucolipotoxicity.” *Obesity (Silver Spring)* 18 (9): 1695–700. doi:10.1038/oby.2009.510.

Millan MJ, Andrieux, A, Bartzokis, G, Cadenhead, K, Dazzan, P, Fusar-Poli, P, Gallinat, J, Giedd, J, Grayson, DR, Heinrichs, M, Kahn, R, Krebs, MO, Leboyer, M, Lewis, D, Marin, O, Marin, P, Meyer-Lindenberg, A, McGorry, P, McGuire, P, Owen, MJ, et al. 2016. “Altering the course of schizophrenia: progress and perspectives.” *Nat Rev Drug Discov* 15 (7): 485–515. doi:10.1038/nrd.2016.28.

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. 2011. “Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects.” *Biol Psychiatry* 70 (7): 663–71. doi:10.1016/j.biopsych.2011.04.013.

Miller, RG. 1981. *Simultaneous Statistical Inference.* 2. New York: Springer-Verlag.

Misiak B, Stańczykiewicz B, Łaczmański Ł, Frydecka D. 2017. “Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis.” *Schizophr Res.* 190: 18–27. doi:10.1016/j.schres.2017.03.031.

Mitra S, Natarajan R, Ziedonis D, Fan X. 2017. “Antioxidant and anti-inflammatory nutrient status, supplementation, and mechanisms in patients with schizophrenia.” *Prog Neuropsychopharmacol Biol Psychiatry.* 78: 1–11. doi:10.1016/j.pnpbp.2017.05.005.

Mowry BJ, Nancarrow DJ. 2001. “Molecular genetics of schizophrenia.” *Clin Exp Pharmacol Physiol.* 28 (1–2): 66–9.

Muller N, Riedel M, Ackenheil M, Schwarz MJ. 1999. “The role of immune function in schizophrenia: An overview.” *Eur Arch Psychiatry Clin Neurosci.* 249 (Suppl 4): 62–8.

Muoio DM, Koves TR. 2007. “Lipid-induced metabolic dysfunction in skeletal muscle.” *Novartis Found. Symp.* 24–38; discussion 38–46, 196–203.

Muoio DM, Neufer PD. 2012. “Lipid-induced mitochondrial stress and insulin action in muscle.” *Cell Metab.* 15 (5): 595–605. doi:10.1016/j.cmet.2012.04.010.

Muoio DM, Noland RC, Kovalik JP, Seiler SE, Davies MN, DeBalsi KL, Ilkayeva OR, Stevens RD, Kheterpal I, Zhang J, Covington JD, Bajpeyi S, Ravussin E, Kraus W, Koves TR, Mynatt RL. 2012. “Muscle-specific deletion of carnitine acetyltransferase compromises glucose tolerance and metabolic flexibility.” *Cell Metab.* 15 (5): 764–77. doi:10.1016/j.cmet.2012.04.005.

Murray RM, Lewis SW. 1987. “Is schizophrenia a neurodevelopmental disorder?” *Br Med J (Clin Res Ed).* 19;295 (6600): 681–2.

Murray, PJ. 2006. “Understanding and exploiting the endogenous interleukin-10/STAT3-mediated anti-inflammatory response.” *Curr. Opin. Pharmacol.* 6 (4): 379–86.

Möller, HJ. 2007. “Clinical evaluation of negative symptoms in schizophrenia.” *Eur Psychiatry.* 22 (6): 380–6. doi:10.1016/j.eurpsy.2007.03.010.

Müller N, Schwarz MJ. 2010. “Immune System and Schizophrenia.” *Curr Immunol Rev.* 6 (3): 213–20.

Müller N, Weidinger E, Leitner B, Schwarz MJ. 2015. “The role of inflammation in schizophrenia.” *Front Neurosci.* 9: 372. doi:10.3389/fnins.2015.00372.

Na KS, Kim YK. 2007. “Monocytic, Th1 and th2 cytokine alterations in the pathophysiology of schizophrenia.” *Neuropsychobiology* 56 (2–3): 55–63.

Naudin J, Mege JL, Azorin JM, Dassa D. 1996. “Elevated circulating levels of IL-6 in schizophrenia.” *Schizophr. Res.* 20 (3): 269–273.

Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, Rochon J, Gallup D, Ilkayeva O, Wenner BR, Yancy WS Jr, Eisenson H, Musante G, Surwit RS, Millington DS, Butler MD, Svetkey LP. 2009. “A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance.” *Cell Metab.* 9 (4): 311–26. doi:10.1016/j.cmet.2009.02.002.

Ng F, Berk M, Dean O, Bush AI. 2008. “Oxidative stress in psychiatric disorders: evidence base and therapeutic implications.” *Int J Neuropsychopharmacol.* 11 (6): 851–76. doi:10.1017/S1461145707008401.

NIMH, National Institute of Mental Health. 2015. Accessed March 1, 2017. http://www.nimh.nih.gov/health/statistics/prevalence/schizophrenia.shtml.

Noland RC, Koves TR, Seiler SE, Lum H, Lust RM, Ilkayeva O, Stevens RD, Hegardt FG, Muoio DM. 2009. “Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control.” *J Biol Chem.* 284 (34): 22840–52. doi:10.1074/jbc.M109.032888.

Nordberg J, Arnér ES. 2001. “Reactive oxygen species, antioxidants, and the mammalian thioredoxin system.” *Free Radic Biol Med.* 31 (11): 1287–312.

Noto C, Ota VK, Gadelha A, Noto MN, Barbosa DS, Bonifácio KL, Nunes SO, Cordeiro Q, Belangero SI, Bressan RA, Maes M, Brietzke E. 2015. “Oxidative stress in drug naïve first-episode psychosis and antioxidant effects of risperidone.” *J Psychiatr Res.* 68: 210–6. doi:10.1016/j.jpsychires.2015.07.003.

Patel S, Sharma D, Kalia K, Tiwari V. 2017. “Crosstalk between endoplasmic reticulum stress and oxidative stress in schizophrenia: The dawn of new therapeutic approaches.” *Neurosci Biobehav Rev.* 83: 589–603. doi:10.1016/j.neubiorev.2017.08.025.

Pawełczyk T, Grancow M, Kotlicka-Antczak M, Trafalska E, Gębski P, Szemraj J, Żurner N, Pawełczyk A. 2015. “Omega-3 fatty acids in first-episode schizophrenia – a randomized controlled study of efficacy and relapse prevention (OFFER): rationale, design, and methods.” *BMC Psychiatry* 2;15:97. doi:10.1186/s12888-015-0473-2.

Pawełczyk T, Grancow-Grabkab M, Trafalskac E, Szemrajd J, Pawełczyk A. 2017. “Oxidative stress reduction related to the efficacy of n-3 polyunsaturated fatty acids in first episode schizophrenia: Secondary outcome analysis of the OFFER randomized trial.” *Prostaglandins Leukot Essent Fatty Acids.* 121: 7–13. doi:10.1016/j.plefa.2017.05.004.

Pepys MB, Hirschfield GM. 2003. “C-reactive protein: a critical update.” *J Clin Invest.* 111 (12): 1805–12.

Perry BI, McIntosh G, Weich S, Singh S, Rees K. 2016. “The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis.” *Lancet Psychiatry.* 3 (11): 1049–1058. doi:10.1016/S2215-0366(16)30262-0.

Petrikis P, Voulgari PV, Tzallas AT, Archimandriti DT, Skapinakis P, Mavreas V. 2015. “Cytokine profile in drug-naïve, first episode patients with psychosis.” *J Psychosom Res.* 79 (4): 324–7. doi:10.1016/j.jpsychores.2015.06.011.

Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. 2017. “Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis.” *JAMA Psychiatry.* 74 (3): 261–269. doi:10.1001/jamapsychiatry.2016.3803.

Polymeropoulos MH, Licamele L, Volpi S, Mack K, Mitkus SN, Carstea ED, Getoor L, Thompson A, Lavedan C. 2009. “Common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol supports a key role of lipid homeostasis in.” *Schizophr. Res* 108: 134−142.

Potvin S, Stip E, Sepehry AA, et al. 2008. “Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review.” *Biol Psychiatry* 63: 801–8.

Ptolemy AS, Rifai N. 2010. “What is a biomarker? Research investments and lack of clinical integration necessitate a review of biomarker terminology and validation schema.” *Scand J Clin Lab Invest Suppl.* 242: 6–14. doi:10.3109/00365513.2010.493354.

Quinones MP, Kaddurah-Daouk R. 2009. “Metabolomics tools for identifying biomarkers for neuropsychiatric diseases.” *Neurobiol Dis* 35 (2): 165–76.

Raffa M, Mechri A, Othman LB, Fendri C, Gaha L, Kerkeni A. 2009. “Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients.” *Prog. Neuropsychopharmacol Biol. Psychiatry.* 33 (7): 1178–83. doi:10.1016/j.pnpbp.2009.06.018.

Ramsay RR, Gandour RD, van der Leij FR. 2001. “Molecular enzymology of carnitine transfer and transport.” *Biochim Biophys Acta.* 1546 (1): 21–43.

Rastad C, Martin C, Asenlöf P. 2014. “Barriers, benefits, and strategies for physical activity in patients with schizophrenia.” *Phys Ther.* 94 (10): 1467–79. doi:10.2522/ptj.20120443.

Reddy RD, Yao JK. 1996. “Free radical pathology in schizophrenia: a review.” *Prostaglandins Leukot Essent Fatty Acids.* 55 (1–2): 33–43.

Reuter SE, Evans AM. 2012. “Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects.” *Clin Pharmacokinet.* 51 (9): 553–72. doi:10.2165/11633940-000000000-00000.

Riegel RE, Valvassori SS, Moretti M, Ferreira CL, Steckert AV, de Souza B, Dal-Pizzol F, Quevedo J. 2010. “Intracerebroventricular ouabain administration induces oxidative stress in the rat brain.” *Int J Dev Neurosci.* 28 (3): 233–7. doi:10.1016/j.ijdevneu.2010.02.002.

Ripke and Schizophrenia Working Group of the Psychiatric Genomics Consortium. 2014. “Biological Insights From 108 Schizophrenia-Associated Genetic Loci.” 421–427. doi:10.1038/nature13595.

Rizza S, Copetti M, Rossi C, Cianfarani MA, Zucchelli M, Luzi A, Pecchioli C, Porzio O, Di Cola G, Urbani A, Pellegrini F, Federici M. 2014. “Metabolomics

signature improves the prediction of cardiovascular events in elderly subjects." *Atherosclerosis.* 232 (2): 260–4. doi:10.1016/j.atherosclerosis.2013.10.029.

Rutkowsky JM, Knotts TA, Ono-Moore KD, McCoin CS, Huang S, Schneider D, Singh S, Adams SH, Hwang DH. 2014. "Acylcarnitines activate proinflammatory signaling pathways." *Am. J. Physiol. Endocrinol. Metab.* 306 (12): E1378−87. doi:10.1152/ajpendo.00656.2013.

Sampey BP, Freemerman AJ, Zhang J, Kuan PF, Galanko JA, O'Connell TM, Ilkayeva OR, Muehlbauer MJ, Stevens RD, Newgard CB, Brauer HA, Troester MA, Makowski L. 2012. "Metabolomic profiling reveals mitochondrial-derived lipid biomarkers that drive obesity-associated inflammation." *PLoS One.* 7 (6): e38812. doi:10.1371/journal.pone.0038812.

Samuel VT, Shulman GI. 2012. "Mechanisms for insulin resistance: common threads and missing links." *Cell.* 148 (5): 852–71. doi:10.1016/j.cell.2012.02.017.

Sarandol A, Sarandol E, Acikgoz HE, Eker SS, Akkaya C, Dirican M. 2015 . "First-episode psychosis is associated with oxidative stress: Effects of short-term antipsychotic treatment." *Psychiatry Clin Neurosci.* 69 (11): 699–707. doi:10.1111/pcn.12333.

Scherz-Shouval R, Elazar Z. 2007. "ROS, mitochondria and the regulation of autophagy." *Trends Cell. Biol* 17 (9): 422–7. doi:10.1016/j.tcb.2007.07.009.

Schoenborn JR, Wilson CB. 2007. "Regulation of interferon-gamma during innate and adaptive immune responses." *Adv. Immunol.* 96: 41–101.

Schooneman MG, Vaz FM, Houten SM, Soeters MR. 2013. "Acylcarnitines: reflecting or inflicting insulin resistance?" *Diabetes* 62 (1): 1−8. doi:10.2337/db12-0466.

Schwarz E, Izmailov R, Spain M, Barnes A, Mapes JP, Guest PC, Rahmoune H, Pietsch S, Leweke FM, Rothermundt M, Steiner J, Koethe D, Kranaster L, Ohrmann P, Suslow T, Levin Y, Bogerts B, van Beveren NJ, McAllister G, Weber N, Niebuhr D, Cowan D, Yolken RH. 2010. "Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia." *Biomark Insights.* 5: 39–47.

Sharif K, Vieira Borba V, Zandman-Goddard G, Shoenfeld Y. 2018. "Eppur Si Muove: ferritin is essential in modulating inflammation." *Clin Exp Immunol.* 191 (2): 149–150. doi:10.1111/cei.13069.

Singh OP, Chakraborty I, Dasgupta A, Datta S. 2008. "A comparative study of oxidative stress and interrelationship of important antioxidants in haloperidol and olanzapine treated patients suffering from schizophrenia." *Indian J. Psychiatry.* 50 (3): 171–6. doi:10.4103/0019–5545.43627.

Sirota P, Meiman M, Herschko R, Bessler H. 2005. "Effect of neuroleptic administration on serum levels of soluble IL-2 receptor-alpha and IL-1 receptor antagonist in schizophrenic patients." *Psychiatry Res.* 134 (2): 151–9.

Snyder, SH. 1976. "The dopamine hypothesis of schizophrenia: focus on the dopamine receptor." *Am J Psychiatry.* 133 (2): 197–202.

Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, Harrington A, Ziedonis D, Lv L. 2014. "Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia." *Psychopharmacology (Berl)* 231 (2): 319–25.

Song XQ, Chen XM, Zhang W, Li X, Hei GR, Li YH, Hao YH, Lü LX. 2013. "Study of adiponectin, IL-1β, IL-6 and TNF-α in first episode drug naïve schizophrenia." *Zhonghua Yi Xue Za Zhi.* 93 (41): 3256–60.

Song XQ, Lv LX, Li WQ, Hao YH, Zhao JP. 2009. "The interaction of nuclear factor-kappa B and cytokines is associated with schizophrenia." *Biol. Psychiatry* 65: 481–488.

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Srimal RC, Seth PK, Dikshit M. 2001. "Nitrite content and antioxidant enzyme levels in the blood of schizophrenia patients." *Psychopharmacology (Berl)* 158 (2): 140–5. doi:10.1007/s002130100860.

Steel, N. 2016. "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015." *Lancet* 388 (10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6.

Steiner J, Walter M, Guest P, Myint AM, Schiltz K, Panteli B, Brauner M, Bernstein HG, Gos T, Herberth M, Schroeter ML, Schwarz MJ, Westphal S, Bahn S, Bogerts B. 2010. "Elevated S100B levels in schizophrenia are associated with insulin resistance." *Mol Psychiatry* 15 (1): 3–4. doi:10.1038/mp.2009.87.

Steinke JW, Borish L. 2006. "Cytokines and chemokines." *J Allergy Clin Immunol.* 117 (2 Suppl Mini-Primer): S441–5.

Stojanovic A, Martorell L, Montalvo I, Ortega L, Monseny R, Vilella E, Labad J. 2014. "Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms." *Psychoneuro-endocrinology.* 41: 23–32. doi:10.1016/j.psyneuen.2013.

Suvisaari JM, Saarni SI, Perälä J, Suvisaari JV, Härkänen T, Lönnqvist J, Reunanen A. 2007. "Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey." *J Clin Psychiatry* 68 (7): 1045–55.

Zhang J-M, An J. 2007. "Cytokines, inflammation, and pain." *Int Anesthesiol Clin.* 45 (2): 27–37.

Zhang M, Zhao Z, He L, Wan C. 2010. "A meta-analysis of oxidative stress markers in schizophrenia." *Sci China Life Sci.* 53 (1): 112–24. doi:10.1007/s11427-010-0013-8.

Tandon, R, Nasrallah, HA, Keshavan, MS. 2009. "Schizophrenia, ''just the facts'' 4. Clinical features and conceptualization." *Schizophr. Res.* (110): 1–23.

Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D. 2010. "Weight gain in antipsychotic-naive patients: a review and meta-analysis." *Psychol Med.* 40 (2): 187–200. doi:10.1017/S0033291709990407.

Terlecky SR, Terlecky LJ, Giordano CR. 2012. "Peroxisomes, oxidative stress and inflammation." *World J Biol Chem.* 3 (5): 93–7. doi:10.4331/wjbc.v3.i5.93.

Theodoropoulou S, Spanakos G, Baxevanis CN, Economou M, Gritzapis AD, Papamichail MP, Stefanis CN. 2001. "Cytokine serum levels, autologous mixed lymphocyte reaction and surface marker analysis in never medicated and chronically medicated." *Schizophr Res.* 47 (1): 13–25.

TIBCO Software Inc. 2017. *Statistica (data analysis software system).* version 13. Palo Alto, California. http://statistica.io.

Tourjman V, Kouassi É, Koué MČ, et al. 2013. "Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis." *Schizophr Res.* 151 (1–3): 43–7. doi:10.1016/j.schres.2013.10.011.

Upthegrove R, Manzanares-Teson N, Barnes NM. 2014. "Cytokine function in medication-naive first-episode psychosis: a systematic review and meta-analysis." *Schizophr Res.* 155 (1–3): 101–8. doi:10.1016/j.schres.2014.03.005.

van Kammen DP, McAllister-Sistilli CG, Kelley ME, Gurklis JA, Yao JK. 1999. "Elevated interleukin-6 in schizophrenia." *Psychiatry Res.* 87 (2–3): 129–36.

van Nimwegen LJ, Storosum JG, Blumer RM, Allick G, Venema HW, de Haan L, Becker H, van Amelsvoort T, Ackermans MT, Fliers E, Serlie MJ, Sauerwein HP. 2008. "Hepatic insulin resistance in antipsychotic naive schizophrenic patients: stable isotope studies of glucose metabolism." *J Clin Endocrinol Metab.* 93 (2): 572–7.

Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, O'Donnell CJ, Carr SA, Mootha VK, Florez JC, Souza A, Melander O, Clish CB, Gerszten RE. 2011. "Metabolite profiles and the risk of developing diabetes." *Nat Med.* 17 (4): 448–53. doi:10.1038/nm.2307.

Watanabe Y, Someya T, Nawa H. 2010. "Cytokine hypothesis of schizophrenia pathogenesis: evidence from human studies and animal models." *Psychiatry Clin Neurosci.* 64 (3): 217–30. doi:10.1111/j.1440-1819.2010.02094.x.

Vaughan, DE. 2005. "PAI-1 and atherothrombosis." *Journal of Thrombosis and Haemostasis* 3 (8): 1879–83. doi:10.1111/j.1538-7836.2005.01420.x.

Weinberger, DR. 1987. "Implications of normal brain development for the pathogenesis of schizophrenia." *Archives of General Psychiatry* 44: 660–669.

Velthorst E, Nelson B, Wiltink S, de Haan L, Wood SJ, Lin A, Yung AR. 2013. "Transition to first episode psychosis in ultra high risk populations: does baseline functioning hold the key?" *Schizophr Res.* 143 (1): 132–7. doi:10.1016/j.schres.2012.10.025.

Windgassen EB, Funtowicz L, Lunsford TN, Harris LA, Mulvagh SL. 2011. "C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians." *Postgrad. Med.* 123 (1): 114–119. doi:10.3810/pgm.2011.01.2252.

World Health Organization. 1992. *The ICD–10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines.* Geneva, Switzerland.

Wu X, Huang Z, Wu R, Zhong Z, Wei Q, Wang H, Diao F, Wang J, Zheng L, Zhao J, Zhang J. 2013. "The comparison of glycometabolism parameters and lipid profiles between drug-naive, first-episode schizophrenia patients and healthy controls." *Schizophr Res* (150): 157–162.

Vuksan-Cusa B, Sagud M, Jakovljevic M. 2010. "C-reactive protein and metabolic syndrome in patients with bipolar disorder compared to patients with schizophrenia." *Psychiatr Danub.* 22 (2): 275–7.

Vuksan-Cusa B, Sagud M, Jakovljevic M, Peles AM, Jaksic N, Mihaljevic S, Zivkovic M, Mikulic SK, Jevtovic S. 2013. "Association between C-reactive protein and homocysteine with the sub-components of metabolic syndrome in stable patients with bipolar disorder and schizophrenia." *Nord J Psychiatry.* 67 (5): 320–5. doi:10.3109/08039488.2012.745601.

Yao JK, Keshavan MS. 2011. "Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view." *Antioxid Redox Signal.* 15 (7): 2011–35. doi:10.1089/ars.2010.3603.

Yao JK, Leonard S, Reddy RD. 2006. "Altered glutathione redox state in schizophrenia." *Dis Markers.* 22 (1–2): 83–93.

Yao JK, Magan S, Sonel AF, Gurklis JA, Sanders R, Reddy RD. 2004. "Effects of omega-3 fatty acid on platelet serotonin responsivity in patients with schizophrenia." *Prostaglandins Leukot Essent Fatty Acids.* 71 (3): 171–6. doi:10.1016/j.plefa.2004.03.011.

Yegin A, Ay N, Aydin O, Yargici N, Eren E, Yilmaz N. 2012. “Increased oxidant stress and inflammation in patients with chronic schizophrenia.” *Int. J. Clin. Med.* 3 (5): 368–376. doi:10.4236/ijcm.2012.35070.

Yung AR, McGorry PD. 1996. “The initial prodrome in psychosis: descriptive and qualitative aspects.” *Aust N Z J Psychiatry* 30 (5): 587–99.

Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. 1996. “Monitoring and care of young people at Incipient risk of psychosis.” *Schizophr Bull* 22 (2): 283–303.

SUMMARY IN ESTONIAN

Atsüülkarnitiinide, põletiku ja oksüdatiivse stressi määra kajastavate biomarkerite profiilid esmase psühhoosiepisoodiga patsientidel enne ja pärast antipsühhootilist ravi

Skisofreeniaspektri häired avalduvad esmase psühhootilise episoodiga enamasti noores täiskasvanueas. Psühhoosi puhul võivad kliinilises pildis ilmneda erinevad sümptomid, mis on iseloomulikud ka skisofreeniale, nagu näiteks taju-, mõtlemis-, tunde- ja tahteelu häired. Psühhootiliste häirete põhjus on bioloogiliste protsesside häirumine ajus, mis on tihedalt seotud organismi üldiste metaboolsete muutusega, sh ka põletiku ja/või oksüdatiivse stressi markerite muutusega. Varasemad uuringud kinnitavad, et skisofreeniaspektri häired ja metaboolne sündroom ühes suhkru- ja lipiidide ainevahetushäiretega on omavahel tihedalt seotud. Samas puudub ühtne seisukoht, et kuivõrd metaboolne düsregulatsioon krooniliste psühhootiliste häirete puhul on omistatav haigusele enesele või antipsühhootlise ravi kõrvalmõjudele. Antud küsimusele võimaldab vastuseid pakkuda esmase psühhoosiepisoodiga patsientide vereseerumist eraldatavate biomarkerite tasemete uurimine enne antipsühhootlise ravi alustamist ja ravi kohaldamise järgselt.

Esmase psühhoosiepisoodiga patsientidel läbiviidud uuringud on leidnud glükoosi taluvuse langust, insuliini taseme tõusu ning metaboolseid muutusi juba enne ravi algust antipsühootikumidega. Atsüülkarnitiinid on rasvhapete beetaoksüdatsiooni vaheproduktid, mille lagundamise tulemusena mitokondriaalses maatriksis tekivad ketokehad. Atsüülkarnitiinide biokeemiline analüüs võimaldab määrata mitokondrite funktsiooni ning rasvhapete oksüdatsiooniga seotud ensüümide häireid, kuna see põhjustab pikaahelaliste atsüülkarnitiinide kuhjumist verre, mis omakorda aktiveerib põletikumediaatorite vabanemist ning mõjutab insuliini resistentsuse teket. Põletikumarkerite profiil võib olla seotud patsiendi kliinilise staatusega ja muutused selles võivad olla seotud antipsühhootilise ravi toimega. Samas on muutusi põletikumarkerite tasemes täheldatud nii kroonilise skisofreenia kui ka emase psühhoosiepisoodiga patsientidel, kes pole veel antipsühhootilist ravi saanud. Põletikumarkereid sekreteerivad organismis erinevad rakud, mis on seotud immunoloogilise ja põletikulise vastuse tekkega füsioloogilistes ja patoloogilistes tingimustes. Tsütokiinide hulka kuuluvad erinevad põletikku vahendavad valgud nagu interleukiinid, interferoonid, tuumornekroosifaktorid, transformeerivad kasvufaktorid ja kemokiinid. Antipsühhootiline ravi omab positiivset mõju haigussümptomitele ning lisaks tekitab muutusi põletikumarkerite profiilis, alandades üldist põletiku taset. Erinevate uuringute tulemusena pole aga teadlased leidnud konsensust, millised on konkreetsed skisofreenia või esmase psühhootilise episoodiga seotud verest määratavad diagnostilised põletikumarkerid ja millised muutused biomarkerite tasemetes haiguse erinevates staadiumites aset leiavad.

Oksüdatiivse stressi puhul saavutavad prooksüdandid (reaktiivsed hapniku, lämmastiku osakesed ja vabad radikaalid, nagu lipiidide peroksüül- ja alkok-

süülradikaalid jt) ülekaalu antioksüdantide üle ning sellest tekkiv redoksstaatuse muutus põhjustab rakkude kahjustust, patofüsioloogilisi protsesse nagu põletik, lipiidide peroksüdatsioon, mitokondrite düsfunktsionaalsus jt, mis tekitavad muutusi organismi homöostaasis. Oksüdatiivse stressi staatuse hindamiseks tuleb mõõta mitmeid biomarkereid. Paraku on andmed oksüdatiivse stressi olemasolu kohta skisofreeniaspektri häire erinevate staadiumite puhul vasturäägivad. Mitmed uuringud on raporteerinud muutustest antioksüdantsete ensüümide osas, kuid oksüdatiivse stressi allika (lipiidide või valkude peroksüdatsioonist tingitud) ja määra (*low-grade, high-grade*) osas on uuringutulemused olnud varieeruvad.

Psühhootiliste häirete puhul on kaasaegsete uuringute ja kliiniliste ravistrateegiate rakendamise eesmärk varajane ennetamine ja/või sekkumine, mis aitab kaasa haiguse paremale prognoosile ja toetab paranemist. Erinevate psühhootiliste häirete sümptomite sarnasus ning komplekssus muudab aga diagnoosimise keerukaks. Eelnevat arvesse võttes on oluline uurida psühhootiliste haiguste molekulaarseid mehhanisme ja raviga kaasnevaid muutusi ning töötada välja objektiivsed diagnostilised biomarkerite paketid, mis võimaldaks skisofreeniaspektri häireid diagnoosida haiguse varasemas staadiumis, häire olemust paremini mõista ning kohaldada efektiivset ja võimalusel individuaalset ravi.

Uurimistöö eesmärgid

Antud doktoritöö üldine eesmärk oli uurida atsüülkarnitiinide profiili, põletiku ja oksüdatiivse stressi taseme määra ning osakaalu esmase psühhoosiepisoodiga patsientidel enne ja pärast antipsühhootilist ravi ning analüüsida andmeid põletiku ja oksüdatiivse stressi taseme ning atsüülkarnitiinide muutuste kohta seitsmekuulise antipsühhootilise ravi jooksul.

Uuringu täpsemad eesmärgid:

1. selgitada, millised on muutused atsüülkarnitiinide tasemetes esmase psühhoosiepisoodiga patsientidel enne ja pärast seitsmekuulist antipsühhootilist ravi;
2. määrata põletikumarkerite tase esmase psühhoosiepisoodiga patsientidel enne ja pärast seitsmekuulist antipsühhootilist ravi;
3. selgitada, milline on oksüdatiivse stressi osakaal esmase psühhoosiepisoodiga patsientidel enne ja pärast seitsmekuulist antipsühhootilist ravi;
4. määratleda üldised muutused mõõdetud biomarkerite lõikes esmase psühhoosiepisoodiga patsientidel enne ja pärast seitsmekuulist antipsühhootilist ravi.

Uuritavad ja meetodid

Uuringu läbiviimine oli kooskõlastatud Tartu Ülikooli inimuuringute eetika komiteega ning kõik uuritavad andsid kirjaliku informeeritud nõusoleku uuringus osalemiseks. Uuritavaid patsiente oli kokku 38 (21 meest ja 17 naist) ning nad olid pöördunud esmase psühhoosiepisoodi avaldumise järgselt ravile Tartu

Ülikooli Kliinikumi Psühhiaatriakliinikusse. Uuringusse kaasamiseks pidid patsiendid vastama järgmistele kriteeriumitele: vanus 18–45 eluaastat; esmase, psühhiaatri poolt diagnoositud psühhoosiepisoodi avaldumine; ravimata psühhoosi kestus alla 3 aasta; polnud varasemalt (kuni esmase psühhoosiepisoodini) saanud ravi antipsühhootikumidega. Patsiente ei kaasatud uuringusse, kui nad vastasid ühele järgnevatest väljaarvamiskriteeriumitest: muu meditsiinilise põhjusega psühhoos või uimastite /illegaalsete psühhoaktiivsete ainete tarvitamisest tingitud psühhoos. Esmase psühhoosiepisoodi diagnoos põhines kliinilisel intervjuul vastavalt Rahvusvahelisele Haiguste klassifikatsiooni 10. väljaandele (RHK-10).

Kontrollgrupp kaasati uuringusse samast geograafilisest piirkonnast, kust esmase psühhoosiepisoodiga patsiendid, see koosnes 37 vaimselt tervest vabatahtlikust (16 meest ja 21 naist), kes statistiliselt ei erinenud vanuse ega soo poolest uuritavatest patsientidest. Kontrollgruppi valitud isikuid intervjueerisid kogenud psühhiaatrid, et välistada vaimsete häiretega isikute kaasamist. Välistavaks tingimuseks oli kontrollgruppi kuuluvate isikute puhul ka psühhootiliste häirete esinemine nende lähisugulastel. Uuritavate kaasamise puhul ei olnud välistavateks kriteeriumiteks suitsetamine ja/või narkootikumide varasem tarvitamine anamneesis.

Uuring koosnes kahest faasist: kaasamisperiood (haiglasse sattumisel) ja järelfaas (kestusega 7.18 ± 0.73 kuud). Esmase psühhoosiepisoodiga patsientidel koguti tühja kõhuga võetud vereproovid, kliinilised ja demograafilised andmed ja kehamassiindeks (KMI) eelpool nimetatud kahel visiidil. Haigussümptomite raskust hinnati kasutades Positiivsete ja negatiivsete sümptomite skaalat (PANSS). Füüsiline läbivaatus koosnes KMI hindamisest. Kontrollgrupi puhul koguti vereproovid, demograafilised andmed ning hinnati KMI.

Biokeemiliste markerite määramisel kasutati tänapäevaseid rahvusvaheliselt aktsepteeritud määramismeetodeid [voogsisestusanalüüs (FIA, *flow injection analysis*), vedelikkromatograafia ja tandem-massispektomeetria kombinatsiooni, *sandwich* kemoluminestsents-immuunmeetodit ja fotokolorimeetria tehnikaid].

Tulemused ja järeldused

1. Ravieelselt oli esmase psühhoosiepisoodiga patsientidel võrreldes kontrollgrupiga pikaahelaliste atsüülkarnitiinide (C14:1, C16, C16:1 and C18:1) tase seerumis tõusnud ja lühikeseahelalise atsüülkarnitiini (C3) tase langenud. Antipsühhootilise ravi tulemusena taandusid muutused atsüülkarnitiinide tasemetes kontrollgrupi tasemele. Erinevalt lühikeseahelalistest atsüülkarnitiinidest oli pikaahelaliste atsüülkarnitiinide teke karnitiini kaudu soodustatud, mis viitab madalatasemelisele (*low-grade*) kroonilisele põletikulisele seisundile esmase psühhoosiepisoodiga patsientidel, mida aga seitsmekuuline antipsühhootiline ravi suutis korrigeerida/neutraliseerida.
2. Võrreldes kontrollgrupiga oli esmase psühoosiepisoodiga patsientidel tõusnud teatud põletikumarkerite (ferritiini, PAI-1 ja IL-6) tase. Seitsmekuulise

antipsühhootilise ravi tulemusena langes patsientide grupis kõige enam ferritiini tase, millele järgnes IL-1α. Ferritiini, TNF-α, PAI-1 ja IL-6 tasemed taastusid kontrollgrupi tasemele, mis on tõenduseks madalatasemelisest krooniliset põletikust esmase psühhoosiepisoodi ajal ning mille puhul antipsühhootiline ravi omas soodsat mõju põletiku neutraliseerimisel.

3. Esmase psühhoosiepisoodiga patsientidel ei esinenud uuringusse kaasamise hetkel oksüdatiivse stressiga seotud parameetrites olulisi erinevusi võrreldes kontrollgrupiga. Seitsmekuulise antipsühhootilise ravi tulemusena vähenes patsientide grupis valkude ja lipiidide peroksüdatsiooni määr, mis on seostatav antipsühhootikumide positiivse mõjuga üldisele oksüdatiivse stressi tasemele.
4. Kokkuvõtvalt näitasid eelpool toodud tulemused seda, et esmane psühhoosiepisood on seotud madalatasemelise kroonilise põletikulise seisundiga, millega kaasnevad muutused lipidoomikas (atsüülkarnitiinides), kuid samal ajal ei esine märkimisväärset erinevust oksüdatiivse stressi tasemes võrreldes kontrollgrupiga. Seitsmekuulise antipsühhootilise ravi tulemusena alaneb põletiku ja oksüdatiivse stressi tase ning muutused atsüülkarnitiinides normaliseeruvad kontrollgrupi tasemele. Vaatamata nimetatud positiivsetele toimetele, toob antipsühhootiline ravi juba haiguse varajases staadiumis kaasa ebasoovitavad metaboolsed nihked.

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Balõtšev R, Haring L, Koido K, Leping V, Kriisa K, Zilmer M, Vasar V, Piir A, Lang A, Vasar E. 2017. "Antipsychotic treatment is associated with inflammatory and metabolic biomarkers alterations among first-episode psychosis patients: A 7-month follow-up study." *Early Interv Psychiatry.* doi: 10.1111/eip.12457

Kriisa K, Haring L, Vasar E, Koido K, Janno S, Vasar V, Zilmer K, Zilmer M. Antipsychotic Treatment Reduces Indices of Oxidative Stress in First-Episode Psychosis Patients. 2016. *Oxid Med Cell Longev*. 2016:9616593.

Leppik L, Kriisa K, Koido K, Koch K, Kajalaid K, Haring L, Vasar E, Zilmer M. 2018. Profiling of Amino Acids and Their Derivatives Biogenic Amines Before and After Antipsychotic Treatment in First-Episode Psychosis. *Front Psychiatry.* 9:155. doi: 10.3389/fpsyt.2018.00155.

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Balõtšev R, Haring L, Koido K, Leping V, Kriisa K, Zilmer M, Vasar V, Piir A, Lang A, Vasar E. 2017. "Antipsychotic treatment is associated with inflammatory and metabolic biomarkers alterations among first-episode psychosis patients: A 7-month follow-up study." *Early Interv Psychiatry*. doi: 10.1111/eip.12457

Kriisa K, Haring L, Vasar E, Koido K, Janno S, Vasar V, Zilmer K, Zilmer M. Antipsychotic Treatment Reduces Indices of Oxidative Stress in First-Episode Psychosis Patients. 2016. *Oxid Med Cell Longev*. 2016:9616593.

Leppik L, Kriisa K, Koido K, Koch K, Kajalaid K, Haring L, Vasar E, Zilmer M. 2018. Profiling of Amino Acids and Their Derivatives Biogenic Amines Before and After Antipsychotic Treatment in First-Episode Psychosis. *Front Psychiatry*. 9:155. doi: 10.3389/fpsyt.2018.00155.

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