Diplomarbeit

Type-II Diabetes in the course of Bipolar Disorder

Correlation between Type-II Diabetes and clinical parameters within Bipolar Disorder

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Christoph Pollak

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(Dr.med.univ.)

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Klinik für Psychiatrie und Psychotherapeutische Medizin

unter der Anleitung von

Assoc-Prof. Priv-Doz. Dr. med. univ. et sci. med. Eva Reininghaus, MBA

&

Dr. med. univ. Frederike Fellendorf

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I. Eidesstattliche Erklärung

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Graz, am 08.07.2018 Christoph Pollak eh

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III. Zusammenfassung

Einleitung: Menschen mit einer bipolaren Erkrankung leiden überproportional häufig auch zusätzlich an somatischen Erkrankungen. Besonders metabolische Störungen wie Übergewicht und Diabetes Mellitus Typ II, assoziiert mit systemischer Entzündung und kognitiven Defiziten zeigen eine hohe Prävalenz und nehmen im Verlauf der Erkrankung zu.

Ziel: In dieser Studie wurde die Prävalenz von Diabetes Mellitus, sowie Nüchtern-Glukosewerten und HbA1c Levels, gemessen bei Menschen mit bipolarer Erkrankung und mit gesunden Kontrollen verglichen. Des Weiteren wurden anhand eines eigens definierten Diabetes Mellitus „Risiko-Score“, Parameter identifiziert welche einen Zusammenhang mit der Entstehung von Diabetes Mellitus im Rahmen der bipolaren Erkrankung haben könnten.

Methode: Im Rahmen der BIPFAT Studie an der Univ.-Klinik für Psychiatrie und Psychotherapeutische Medizin der Medizinischen Universität Graz wurden bei 245 euthymen PatientInnen mit einer bipolaren Erkrankung, und 142 psychisch gesunden Kontrollpersonen Daten zur Medikation, krankheitsspezifischen Parametern, Laborwerten, Body-Mass Index sowie Rauchen und Bewegungsverhalten erhoben. Es wurden Unterschiedsberechnungen zwischen Erkrankten und Gesunden sowie Korrelationen des Risiko-Scores mit diversen klinischen Parametern durchgeführt.

Ergebnis: Ein positiver Zusammenhang zwischen der bipolaren Erkrankung und erhöhter Prävalenz von Diabetes mellitus im Vergleich zu Kontrollen wurde gezeigt. Des Weiteren wurde berechnet, dass männliche Patienten signifikant mehr Punkte im Diabetes mellitus Risiko-Score erreichten als Frauen. Es zeigte sich ein Zusammenhang zwischen Entzündungsparametern (CRP, IL-6) und einem erhöhten Diabetes mellitus Risiko-Score. Bei weiteren berechneten Faktoren wie dem Glukose Metabolismus, Lebensstilfaktoren (Rauchen, Bewegung), medikamentöser Therapie und der klinischen Klassifikation (Bipolar I versus II) konnten keine Korrelate festgestellt werden.

Diskussion: Zusammenfassend kann gesagt werden, dass PatientInnen mit einer bipolaren Erkrankung ein erhöhtes Risiko haben an Diabetes mellitus Typ II zu erkranken. Chronische Entzündung, sowie das Geschlecht scheinen dabei eine Rolle zu spielen.
Da das Vorliegen eines Diabetes mellitus mit einer erhöhten Mortalität verbunden ist, sollte bereits präventiv einer manifesten Erkrankung vorgebeugt werden und ein Screening frühzeitig erfolgen.

IV. Abstract

Introduction: People with bipolar disorder suffer from comorbid somatic disorders with disproportional frequency. Metabolic disorders such as overweight and diabetes mellitus in particular, associated with systemic inflammation and cognitive deficits have an especially high prevalence and their occurrence increases during the course of the illness.

Objective: This study analysed the prevalence of diabetes mellitus, fasting glucose and hba1c levels of individuals with bipolar disorder in comparison to mentally healthy controls. Moreover, we aimed to identify parameters which indicate a causal link for diabetes mellitus in the course of a bipolar disorder on the basis of an own defined diabetes mellitus “risk score”.

Methods: Within the scope of the BIPFAT study carried out at the University Hospital of Psychiatry and Psychotherapeutic Medicine of the Medical University of Graz data on medication, disease specific parameters, laboratory test values, body-mass index as also smoking and exercise habits were surveyed in 245 euthymic patients with bipolar disorder and 142 mentally healthy control persons. Furthermore, differences between patients and healthy controls were analysed and correlations between the risk score and several clinical parameters established.

Results: The occurrence of diabetes mellitus was higher in individuals with bipolar disorder compared to the control group. Furthermore, calculations showed that male patients had a significantly higher diabetes mellitus risk score compared to female patients. We found relationship between higher inflammation parameters (CRP, IL-6) and an increased diabetes mellitus risk score in individuals with bipolar disorder. No correlates could be established in the other additional calculated factors such as glucose metabolism, life-style habits (smoking, exercise), medication and clinical classification (bipolar I versus II).

Discussion: In summary, it can be proposed that patients with bipolar disorder have an increased risk of developing diabetes mellitus. Chronic low-grade inflammation as well as gender seems might be associated factors. Since diabetes mellitus is

associated with high mortality rates, a screening should take place at an early stage of bipolar disease in order to prevent the outbreak of a manifest diabetes mellitus.

Content

V. List of abbreviations

DM-RISK-Score……Diabetes Mellitus Risk-Score

DSM-5…...Diagnostic and Statistical Manual of Mental Disorders 5th Revision

HAMD…...Hamilton Rating Scale for Depression

ICD-10…...International Classification of Diseases (10th Revision)

SCID…...Structural Clinical Interview

WHO…...World Health Organisation

YMRS…...Young Mania Rating Scale

CRP……C-Reactive-Protein

HbA1c……Glycated haemoglobin A1c

BIP I……Bipolar I

BIP II……Bipolar II

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1 Introduction

According to lifetime prevalence, approximately 130 000 people in Austria suffer from bipolar-I-disorder and even more from bipolar-II-disorder (1). The disorder is usually diagnosed in late adolescence or early adulthood (1).

Individuals suffering from bipolar disorder seem to have a significantly higher risk of suffering simultaneously mental and somatic comorbidities than it is the case for mentally healthy subjects (2). Especially diabetes mellitus seems to be a frequent comorbidity since it occurs three times as often in individuals suffering from bipolar disorder than in the general healthy population according to the literature (3).

Diabetes mellitus, with its high prevalence in today's society, has become one of the world's leading health issues. According to the World Health Organization report published in 2016, some 422 million people worldwide suffered from diabetes in 2014. 1980 was selected as a comparison year in which 108 million people suffered from diabetes, which expressed in percentage terms represents a 4,7% growth to 8,5% of the world population. This dramatically high number of sufferers and the comorbidities resulting from this situation represent an enormous burden both for society and the health system (4).

That in mind, the question was posed here of what pathophysiological connection could possibly exist in that context. Therefore, a "risk-score" named the diabetes mellitus risk score (DM-RISK-Score), according to the hitherto literature, consisting of different compounds such as demographics, medication and lifestyle, was defined at the research unit for bipolar affective disorders at the Medical University of Graz. In accordance, it was analysed within our cohort to see if our examination matches the postulates of the found literature.

This work is concerned with diabetes and its possible role within the progression of bipolar disorders. My intention here is to provide a survey examining the available literature, illustrating potential relationships and risk-factors between bipolar disorder and diabetes.

2 Theoretical background

In the following I would like to exemplify at first the bipolar disorder and afterwards the diabetes mellitus.

2.1 Bipolar disorder

Bipolar disorder is a complex psychiatric illness and classified with the chapter of affective disorders. Importantly, recent research indicates that bipolar disorders can be seen as a multi-system inflammatory disease (5). Yet, as classified as an affective disorder, it is characterized as to be associated with a change in the emotional state, and thus of the overall mood. The bipolar disorders, which are widely referred to by many people as manic-depressive illnesses, are characterized by abrupt changes of mood into the category of depression as well as (hypo)mania. Periods free of mood symptoms are classified as euthymic episodes (1).

2.1.1 Clinical aspects

The lifetime prevalence of episode(s) of hypomania/mania can be cited as a significant characteristic by means of which bipolar disorder can be distinguished from unipolar depressive disorder. As a consequence, the diagnosis of bipolar disorder can only be made when it is apparent from the case history that the patient has experienced at least one episode of hypomania and/or mania (1). For the sake of clarity, I want to present here all the criteria leading to depression, mania or also hypomania, which are relevant in establishing the diagnosis.

2.1.1.1 Bipolar depression criteria

Importantly, almost always over two weeks the symptoms listed beneath persist (1).

- At least two of the following main criteria:
    - a continued depressive mood
    - loss of interest and joylessness/ anhedonia in activities, which

are otherwise experienced as pleasurable
    - reduced energy or increased fatigability
- at least one of the following criteria (sum of main and side-criteria: depending on severity 4-8 criteria)
    - a feeling of being worthless or unreasonable
    - feelings of guilt
    - recurring thoughts about death or suicide
    - a reduced capacity for thinking, making decisions or concentration
    - psychomotor restlessness or slowdown
    - sleeping disorders
    - loss or gain of appetite
- The depression is not triggered by a grief reaction, organic causes or substance abuse

2.1.1.2 Mania criteria

- The mood is euphoric/raised and/or irritable for at least a week or the symptoms make a hospital admission essential.

At least three of the following criteria (in the case of euphoric/raised mood) or four (in the case of irritable mood):

- increased activity/psychomotor restlessness
- constant urge to speak/logorrhoea
- a flood of ideas or a subjective racing thoughts sensation
- reduced sleep requirement
- extremely high self-assessment through to megalomania
- distractibility/continuous changes in activities and plans
- Loss of normal social inhibitions with accompanying inappropriate conduct and behaviour or an excessive preoccupation with pleasant things and activities, which in all probability will lead to unpleasant consequences, such as for example: reckless shopping sprees, amazing of debt, risky car

driving, increased libido. The behaviour patterns given here and the criteria referred to previously represent an impairment to both the professional and social life of the affected person and frequently make a hospital stay a necessity, above all when these are accompanied by distinctly psychotic symptoms.

In order to diagnose bipolar disorder, the psychotic symptoms must occur exclusively during the phases or alternatively shortly maximum within two weeks after their occurrence. The trigger for the mania must not lie either in organic causes or in substance abuse (1).

2.1.1.3 Hypomania criteria

- The mood is euphoric/raised or irritable for a period of at least four days.

At least three of the following (in the case of euphoric/raised mood) or four (in the case of an irritable mood) criteria are given:

- increased activity or motoric restlessness
- constant urge to speak/logorrhoea
- reduced sleep requirement
- readiness to be distracted or difficulties in concentrating
- excessive shopping or frivolous/ irresponsible behaviour
- increased libido
- increased sociability.

The criteria listed above are not related to an impairment of the professional or social life of the affected person, they do not make a hospital stay a necessity, nor do they occur in the context of psychotic symptoms.

2.1.2 Epidemiology

The lifetime prevalence is put at between three and five % (2). Bipolar disorder often begins in adolescence and early adulthood, this was shown by a population random sample that collected the incidence over a period of ten years including patients between fourteen and twenty-four years of age. In this sample group there was a cumulative 2,9% for manic, four % for hypomanic, 29,4% for depressive and 19% for sub-depressive episodes (6) Furthermore, it should be noted that there are no gender differences in the frequency of occurrence. The peak for the first occurrence of the diagnosis of disease is on average between 25-30 years of age.

Bipolar disorder can present a very wide range of symptoms. The phase duration can vary, in individual cases from a few days up to several months. The depressive and (hypo)manic phases do not always follow on one from the other. The disorder can lead to a deteriorating condition over a period of years, but it can also stay permanently at the same level, or in the case of some individuals the passage of time can lead to a remission (1).

2.1.3 Classification according to aetiology

In clinical use, bipolar disorders can be classified as follows.

2.1.3.1 Bipolar I (BIP I)

When classified as Bipolar I (BIPI), depressive and manic episodes occur in an alternating circular sequence (1).

2.1.3.2 Bipolar II (BIP II)

When classified as Bipolar II (BIPII), depressive and hypomanic phases occur. By definition, no manic episodes are prevalent (1).

2.1.3.3 Bipolar disorder, otherwise specified

Where the patient suffers exclusively from recurrent manic or hypomanic episodes, then this patient is to be classified under ICD-10 as bipolar disorder, otherwise specified (1). One single manic episode without the lifetime prevalence of depression does not allow to classify as bipolar disorder according to the European ICD-10.

2.1.4 Causes and pathogenesis

The pathogenesis of bipolar disorder has not yet been fully understood. A multi-factor genesis of the disease is probable. A central point in this claim is the strong genetic component, which is seen as a probable foundation for an increased susceptibility to this illness. In addition, environmental influences and personality characteristics might also play a decisive role. Despite the knowledge of detailed findings about separate mechanisms involved it has not been possible to derive an integrated aetiopathogenetic model for bipolar disorder from the various research results (2). Furthermore, it has been verified that neurotransmitters such as serotonin and noradrenaline play an important role in the origin and development of bipolar disorder. Psychopharmacological medication can be effective here, in that it can inhibit reuptake from the synaptic cleft or prevent a depletion of transmitters (7).

Occasionally, bipolar disorder occurs during a life crisis or following the occurrence of events with serious emotional repercussions such as the death of a relative, divorce, unemployment or other external stress factors. It has not yet been possible to explain why bipolar disorder can vary in the symptom pattern and in its course from patient to patient, despite specific personal characteristics would appear to play a role. Persons with melancholic and asthenic tendencies, in particular, might be more vulnerable to develop a bipolar disorder (7).

2.1.5 Clinical diagnosis

Clinical observation of the case history and a somatic differential diagnostic approach are essential for establishing the diagnosis of bipolar disorder. This can be a difficult process, above all for the first diagnosis of the disorder. When a patient comes to the doctor in a depressive state then every effort must be made to explore any previous hypomanic or depressive episodes in the case history, insofar as these have occurred. In individuals with hypomanic episodes, and no evident mania, the risk of an incorrect diagnosis exists, for example when unipolar depression is diagnosed for this condition. Especially in the evaluation of hypomanic episodes, an external diagnosis or a third party anamnesis is often useful (1). Also organic clinical pictures,

which can be responsible for the occurrence of maniform conditions, must be ruled out (1).

When there are psychotic symptoms, a stringent differentiation must be made to schizophrenia or a schizoaffective disorder. Megalomania, amorous illusions and paranoia may occur in the case of mania or hypochondriac, nihilistic or guilt delusions in the case of severe depression (2).

Somatic disorders, which can trigger maniform conditions, include for example epilepsy, systemic lupus erythematosus, traumatic brain injury and hyperthyroidism (1). Also pharmaceutical or psychotropic substances can induce maniform conditions such as antibiotics, cocaine and alcohol (1).

2.1.6 Therapy

The therapy of bipolar disorder is based on several principles. In addition to an individual pharmaceutical application, supplementary psychotherapeutic and psycho-educative therapies are recommended (7).

The pharmaceutical therapy consists in the acute treatment of (hypo)manias as well as depressive episodes and the chronic administering of mood stabilizing drugs (1)(7).

In the course of a manic episode hospitalization is most of the cases generally unavoidable. By this means, the damaging effect that can arise from activities provoked by uncritical self-overestimation can be kept within the bounds and prevent harm for both, the patients and their families (1).

Lithium still remains the gold standard as mood stabilizer but also for acute treatment of mania. Nevertheless, in case of dysphoric or irritable mania, for cases of rapid cycling and for mixed episodes atypicals and valproic acids are to be preferred to lithium. In line with evidence-based criteria, the administering of olanzapine, ziprasidone, quetiapine, risperidone and aripiprazole has proved these preparations to have the best values among the group of atypicals in the treatment of manic episodes. Ziprasidone is at present the only substance which has been approved for the treatment of mixed episodes. Initially, in the event of uncooperative behaviour in

the course of a manic episode, the oral or intramuscular administration of aripiprazole, olanzapine, zuclopenthixol or haloperidol may be considered. A supplementary sedation with benzodiazepines (e.g. Lorazepam) is generally also necessary. For mania with psychotic symptoms, a combination treatment with mood stabilizers and atypicals is indicated (1).

2.1.7 Prognosis

Bipolar disorders have a high recurrence rate, although the individuals progression of the disorder is highly variable (8). The majority of patients suffer from few episodes, amounting on average to five. It has been described, however, that 10% of patients experience more than ten episodes (9).

Furthermore, many patients suffer from residual symptoms, which additionally increase the risk of illness relapse (10) and through which permanent negative effects on the social functioning level may result (2).

The following risk factors are known for the course of a serious or chronic course of the disorder:

In the case of frequently recurring episodes:

- early first manifestation
- female gender
- mixed episodes
- serious stress events in life
- psychotic symptoms
- insufficient response to mood stabilizer therapy
- rapid cycling.

In the case of a chronic course:

- frequent episodes
- premorbid personality characteristics with inadequate coping strategies
- insufficient response to the acute and phased prophylactic therapy
- poor compliance

- co-morbid substance abuse
- co-morbidity with other psychiatric or somatic disorders

Bipolar disorder generally leads to bio-psycho-social disadvantages for the one affected. Maintaining or re-establishing social participation is one of the most important objective both for affected patients and also their relatives. Achieving this can often be very difficult, since bipolar disorder in particular is frequently associated with reduced working potential and associated financial consequences or even complete inability to work and an early retirement from employment. This is a depressing situation for those affected, since it prevents adequate social participation and in addition can have a negative influence on the course of the disorder, pertaining a vicious circle (2).

2.1.8 Comorbidities

Patients with serious psychiatric disorders and thus, including patients with bipolar disorder, frequently have increased morbidity and mortality rates when compared with mentally healthy persons (2).

In the following the epidemiologically most significant somatic comorbid diseases are listed weighted by frequency:

- muscular-skeletal diseases 63%
- migraine 35%
- metabolic syndromes and diabetes mellitus 29%
- cardiovascular disease 26%

The percentage of comorbidity as given is over a lifetime (2).

In addition to somatic comorbidities as listed above, special attention must also be paid to psychiatric comorbidities, which are frequently manifested as accompanying symptoms to bipolar disorders.

In the following, the epidemiologically most significant psychiatric comorbid diseases are listed weighted by frequency:

- anxiety 86,7%
    - agoraphobia
    - social phobia

- impulse control disorders 71,2%
    - ADHS
    - Eating disorder
    - personality disorder

- substance abuse and addiction 60,3%
    - alcohol abuse/addiction
    - drug abuse/addiction

The percentage of comorbidity as given is over a lifetime (2).

Comorbidities may play an important factor in resistance to treatment in bipolar disorder. Therefore, it is a clinical imperative to diagnose comorbid disorders when there is occurrence of bipolar disorder, followed by consequent monitoring, induction of preventional strategies and therapy (3).

2.2 Diabetes

Diabetes mellitus is a group of heterogenic diseases with the common characteristic of chronic hyperglycaemia. It is caused either by a default of insulin secretion, insulin effect or the combination of both (11).

2.2.1 Epidemiology

Diabetes mellitus is a worldwide epidemic with an increasing prevalence (11). In Austria the prevalence is estimated to be 6% of the population (12). In Germany, the lifetime prevalence of a manifest diabetes varies depending on age. In the population >50 years it is estimated to be 2-3%, in the >60 years goup it is 15% and in the >70 years group it is 22%. 90% of all patients with diabetes mellitus are suffering from

type-II diabetes and only 5% from type-I. Within the age group < 70 years predominately male individuals suffer from diabetes. The prevalence of type-II diabetes increases with the extent of overeating and lack of exercise. Type-I diabetes also increases continuously with an progressively earlier onset of the disease (11). It can be assumed that this data is also valid for Austria.

2.2.2 Classification according to aetiology

2.2.2.1 Type-I Diabetes Mellitus

Type-I diabetes mellitus is caused by β-cell destruction which leads to total insulin absence (11).

2.2.2.2 Type-II-Diabetes Mellitus

Type-II diabetes mellitus is caused by insulin resistance, secretorial default of β-cells and also of α-cells, caused by a proceeding apoptosis of β-cells and a reduced incretin-secretion and effect (11).

2.2.2.3 Type-III Diabetes

a) Gene defect in the β-cell function
b) Gene defect in the insulin effect
c) Pancreatic illness
d) Endocrine-pathologies
e) Induced by medication e.g.: glucocorticoids, thiazide
f) Immunological
g) Genetic-syndromes (11)

2.2.2.4 Type-IV/Gestations diabetes

Diabetes that occurs during pregnancy (11).

2.2.3 Pathogeneses

Type-I diabetes is caused by an immunological mediated destruction of the β-cells in the insulae pancreaticae leading to autoimmune insulitis with absolute lack of insulin. If 80% of the β-cells are destroyed, the blood sugar rises. Genetic factors play a

predisposing role: 20% of type-I diabetics have a positive family history (with type-I diabetes mellitus) and > 90% of the patients have HLA markers DR 3 and/or DR 4. The following findings support the diagnosis autoimmune insulitis in the case of a freshly established type-I diabetes.:

- Detection of auto anti-bodies(11):
  - Cytoplasmatic islet-cell antibodies (ICA): Antigen: Ganglioside
  - Anti-GAD-Ab (GADA): Antigen: glutamic acid decarboxylase antibodies (GAD65)
  - Anti-IA-2-Ab (IA-2A): Antigen: Tyrosinphosphatase IA-2
  - Insulin-Auto-Ab (IAA): Antigen: (Pro)Insulin
  - Anti-ZnT8-Ab (ZnT8A): zinc-transporters 8

Pathophysiological, several disorders which are listed beneath can play a role in the pathogeneses of **Type-II Diabetes:**

- Disturbed insulin or glucagon secretion: In the type-II diabetic the early phase of the two-peak post prandial insulin secretion is disturbed; this results in post prandial hyperglycaemia. Despite hyperglycaemia, there is additionally a constantly increased glucagon secretion which further enhances hyperglycaemia.
- Apoptosis of the islet-cells (ß-cells): If more than 50% of the islet cells are apoptotic, hyperglycaemia becomes evident
- Reduced incretin secretion and effect
- Decreased insulin action (insulin resistance)
  Cause: Pre-receptor defect, receptor defect with down-regulation,
  Post receptor defect = impairment of intracellular signal transduction,
  e.g. signal transduction of the tyrosine kinases, the RANKL (Receptor Activator of NK-kB-Ligand)

The majority of diseases due to the metabolic syndrome (affluence syndrome or diseases of affluence), which is defined by high occurrence of the four risk factors: visceral obesity, dyslipoproteinemia (triglyceride ↑, HDL-Cholesterol ↓), essential hypertonia and disturbed glucose tolerance and/or type-II diabetes mellitus. At the beginning of the metabolic syndrome, there is an insulin resistance of the insulin dependent tissue (such as in skeletal muscle cells and in the liver), which

requires increased insulin levels for the cellular glucose utilization.
Hyperinsulinemia enhances the feeling of hunger, leads to obesity accelerates and premature arteriosclerosis (11).

2.2.4 Clinical symptoms

The following clinical symptoms can be found in individuals suffering from diabetes:

- Unspecific general symptoms such as fatigue, reduced performance, etc.
- Symptoms as a result of hyperglycaemia and glycosuria with osmotic diuresis: polyuria, thirst, polydipsia, weight loss
- Symptoms caused by disturbances in the electrolyte-and fluid balance: nightly calf cramps, impaired vision, (changing turgor of the eye-lens)
- Skin symptoms:
    - Pruritus
    - Rubeosis diabetica
- Erectile dysfunction, amenorrhea(11)

2.2.5 Long-term effects

Diabetes mellitus favours other complications and illnesses that can occur as a result of the disease:

Angiopathies:

- Macro-angiopathies
    - Coronary heart disease
    - Peripheral artery occlusive disease
- Micro-angiopathies
    - Glomerulosclerosis
    - Retinopathy
    - Neuropathy
    - Small vessel disease
- Diabetic cardiopathies
- Resistance decrease with a tendency to develop bacterial skin and urinary tract diseases, Periodontitis

- Lipid metabolism disorders: Triglyceride ↑, LDL-Cholesterol ↑, HDL-Cholesterol ↓
- Fatty liver,
- Coma diabeticum, hypoglycaemic shock
- Hyporeninaemic Hyperaldosteronisms with hyperkaliaemia, hyponatraemia, hyperchloraemic metabolic acidosis and possible hypotension (11)

2.2.6 Diagnosis

Patients which show clinical symptoms of uncontrolled diabetes mellitus are easily identified as diabetic. Such typical and grave courses can usually only be seen with type-I diabetes. On the contrary, type-II diabetes can often be asymptomatic and be prevalent long before being diagnosed. This is why the German Association of Diabetes recommends the screening of diabetes mellitus in all patients who reach the age of forty-five and older by measuring the fasting-plasma-glucose. Controls are to be repeated all three years. Further people with risk factors (which can be obtained below) should be examined more often (13).

Risk factors for diabetes mellitus are (11):

- Obesity (Body Mass Index (BMI) ≥30,00 kg/m^2)
- Hypertension (RR ≥140/90mmHg)
- Dyslipoproteinemia (Triglycerides (TG) >150/ High Density Lipoprotein (HDL)♂ <35mg/dl, HDL ♀ <45mg/dl)
- Diabetes mellitus of primary relative(s)
- ethnic groups with a high diabetes risk (e.g. Pima-Indians)
- After giving birth to a child with a birth weight of >4.500g
- After gestation diabetes
- Pathologic glucose tolerance/disturbed glucose-homeostasis

Laboratory:

- Fasting-plasma-glucose: Diabetes ≥126mg/dl (≥7,0mmol/l)
- Oral glucose-tolerance-test 2 h-value ≥200mg/dl (≥11,1mmol/l) (e.g. Gestation diabetes)
- Hb long-term blood sugar: Glycated haemoglobin A1c (HbA1c) ≥48 mmol/mol

2.2.7 Therapy

The therapy used for the treatment of diabetes mellitus patients largely depends on the kind of diabetes. A type-I diabetes requires a different therapy than type-II diabetes. A healthy and sensible diet together with a normalization of the weight are indispensable measures and an integral part of the therapy for both types. Another important factor is physical activity since it does not only improve the sensitivity of muscles for insulin but also the insulin mediated glucose uptake. Patient education and controls are an essential component of the therapy. It can also help to exclude or minimize further risk factors such as premature arteriosclerosis and prevent complications.
The choice of the medicine used depends on the type of diabetes, whether the patient is a type-I diabetic or a type-II diabetic, the latter who only partially requires insulin or no insulin at all.
Patients with type-I diabetes mellitus are dependent on a life-long exogenous supply of insulin as of the time when hyperglycaemia occurs. The individual insulin needs orient itself on the physiological insulin secretion and depends on the physiological insulin secretion and the corresponding insulin sensitivity of the person. Under consideration of the remaining function of the β-cells and/or the manifestation of the metabolic dysfunction the daily needs must be adapted continuously (14).

To the extent that you cannot gain control of the impaired glucose metabolism in type-II diabetes with changes in life style such as diet, exercise, weight loss, reduced stress, smoking cessation (15), which is mainly caused by a metabolic syndrome, a medical therapy to reach the individual hba1c target values with oral or injectable diabetes drugs and/or insulin becomes indispensable in order to reduce the probability of macro or micro vascular secondary diseases (16).

2.3 Diabetes and bipolar disorder

Examining the relationship between bipolar disorder and comorbid somatic illnesses is generally difficult, since it is frequently not possible to show whether the bipolar disorder is contingent to another disorder, caused or worsened by one, or again whether it is rooted in a complex interaction of these causes (17).

2.3.1 Prevalence

Literature has described that the prevalence of diabetes mellitus in patients with bipolar disorder is increased (18), especially type-II diabetes mellitus rates are three times higher in patients with bipolar disorder, compared to the general population. Recent studies have estimated that approximately 10% of all patients suffering from bipolar disorder had clear evidence of diabetes mellitus type-II (19). Concerning the risk of cardiovascular mortality, which is the leading cause of death in bipolar patients, diabetes mellitus II is a major contributing factor (20).

2.3.2 Gender

Gender seems to play a distinguishing role, literature suggests that women across all ethnic groups are at higher risk to suffer from glucose and lipid abnormalities, which were found dysregulated at high rates especially in females and over 40 years of age in patients with bipolar disorder (21). Also, obesity which is considered a major risk factor for diabetes mellitus, was highly prevalent (22).

2.3.3 Causes and common disease mechanism

There are several hypotheses trying to link bipolar disorder and diabetes mellitus. Some researchers assume that there is shared pathophysiology linking the two disorders, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, common genetic links, and epigenetic interactions (23). Others hold dysregulations of the purine metabolism as a common link between energy homeostasis and neuro-regulation responsible (24). Further, there have been investigations that thyroid hormone receptor-associated protein 3 (Thrap3) could activate a diabetogenic gene

cascade in adipose cells through interaction with cyclin-dependent kinase 5 (CDK5) subsequently leading to the phosphorylation of peroxisome proliferator-activated receptor γ (PPARγ) at Ser273 (25).

However, also the metabolic syndrome - being a combination of obesity, diabetes mellitus, dyslipidaemia and hypertension - can be understood as an alternative pathomechanism, occurring at high rates in patients with bipolar disorder (26). Nevertheless, despite higher rates of metabolic syndrome in individuals with bipolar disorder, it was in some studies shown that insulin resistance was not increased in patients with bipolar disorder (and prevalent metabolic syndrome). However, they had higher levels of hypertension and abdominal obesity suggesting a reduced capacity to utilize fat as an energy source and implicating that patients with bipolar disorder could be predisposed to exacerbate future weight gain and being at greater risk for diabetes mellitus and cardiovascular disease (27).

Further, unhealthy lifestyle like smoking and lack of physical activity can be held responsible for increasing the risk of developing diabetes mellitus. But also, psychopharmacological medication seems to play a role as it is postulated that lithium, valproic acid and certain atypical antipsychotics, which are used in the treatment of bipolar disorder, may trigger type-II diabetes mellitus by increasing appetite. Especially second generation antipsychotics Olanzapine and Clozapine seem to cause or exacerbate type-II diabetes mellitus even in the absence of overweight (28). According to literature there are differences in the pooled prevalence of diabetes mellitus regarding the different types of clinical classification (19). Also there has been a lot of research focusing on inflammation as common link and factor for the development of type-II diabetes in bipolar disorder (29).

2.3.4 Consequences and outcomes

It has been observed that patients with bipolar disorder and type-II diabetes mellitus suffer a more severe course of illness and are more refractory to treatment (30), lower quality of life, higher prevalence of medical comorbidity and higher cost of illness (31). The control of their diabetes is poorer when compared to patients with diabetes but without bipolar disorder (30). Not only are those irregularities of the glucose metabolism a risk factor for cardio-vascular disorders as mentioned before but also cause damage to the nerves and organs (32). Current research illustrated

that type-II diabetes mellitus has negative effects on brain structure and function. Patients suffering from type-II diabetes mellitus and bipolar disorder indicated a greater morbidity, chronicity and disability plus a lower treatment response to lithium. Bipolar disorder which is accompanied by insulin resistance or type-II diabetes mellitus is associated with smaller hippocampal and cortical grey matter volumes and lower prefrontal N-acetyl aspartate (33). Besides having an impact on the central nervous system, subjects seem to suffer more from impaired learning, memory, and mental flexibility than the general population (34). The treatment of type-II diabetes mellitus and insulin resistance is essential for preserving the brains grey matter and in addition it has positive effects on psychiatric and brain outcomes (33). Therefore, Metformin seems to have the best benefit/risk ratio, and also the dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists and analogues also appear promising. However, these agents have not been specifically studied in populations with mood disorders (30). In contrast, the insulin sensitizer pioglitazone has been well studied and shown to improve symptoms of depression in unipolar or bipolar disorders even in patients without type-II diabetes mellitus or metabolic syndrome (35).

2.4 Questions and hypotheses

Based on the literature research, the following research questions and hypotheses evolved in order to study the association between type-II diabetes mellitus and bipolar disorder.

The prevalence of diabetes mellitus increases with increasing age (36); that in mind, the cohort was separated into two age groups. The German Association of Diabetes recommends the screening of diabetes mellitus in all patients who reach the age of forty-five and older by measuring the fasting-plasma-glucose and it is to be repeated every three years. This is why we chose forty-five to be our cut off for the two age groups, now having one age group younger than forty-five (<45), the other greater or equal forty-five (≥45).

Literature has shown that the risk of diabetes mellitus in patients with bipolar disorder is increased (18). Therefore, the question arises whether patients with bipolar disorder in our cohort have a higher probability of suffering type-II diabetes mellitus

than the general population.

Research question 1: Do patients with bipolar disorder have a higher probability of suffering from diabetes mellitus than the general population (controls)?

Hypothesis 1a: Patients with bipolar disorder suffer more frequently from diabetes mellitus compared to control subjects.

Hypothesis 1b: Patients with bipolar disorder have a higher fasting blood glucose level or an elevated hba1c compared to control subjects.

Due to the prevalence of diabetes mellitus in bipolar patients (32) and the certainty of being at greater risk (23) the question arises if there is a difference in the performance in the Diabetes Mellitus-Risk-Score (DM-Risk-Score) between patients and healthy controls.

Hypothesis 1c: Patients with bipolar disorder have a significantly higher DM-Risk-Score compared to control subjects.

Literature has described a difference in sex in individuals with diabetes mellitus II (21).

Research question 2: Does the prevalence of diabetes mellitus differ between sex in our patient group.

Hypothesis 2a: Women with bipolar disorder suffer more often from diabetes mellitus compared to men with bipolar disorder.

Hypothesis 2b: Women in comparison to men with bipolar disorder have a higher DM-Risk-Score.
Based on found literature there is a connection between unhealthy lifestyle and the risk of developing diabetes mellitus (31)(37).

Research question 3: Is there a connection between unhealthy lifestyle factors and the risk to develop diabetes?

Hypothesis 3a: Patients with bipolar disorder who smoke have a higher DM-Risk-Score compared to patients who do not smoke.

Hypothesis 3b: Patients with bipolar disorder with low physical activity reach a higher DM-Risk-Score compared to patients with moderate activity and patients with moderate activity reach a higher DM-Risk-Score compared to people with high activity.

Based on the current literature, there seems to be an association between the administration of psychotropic pharmaceuticals and the occurrence of diabetes mellitus in the treatment of bipolar disorder (38). There are differences in patients receiving Lithium, antipsychotics, Lamotrigine, valproic acid and combined medication (more than two different pharmaceuticals) in the DM-Risk-Score.

Research question 4: Are there differences between groups of pharmaceuticals in the DM-Risk-Score?

Hypothesis 4a: Patients receiving antipsychotics reach a higher DM-Risk-Score compared to patients receiving lithium. Patients receiving Lithium reach a higher DM-Risk-Score compared to people receiving valproic acid. Patients receiving valproic acid reach a higher DM-Risk-Score compared to people receiving combined medication. Patients receiving combined medication reach a higher DM-Risk-Score compared to people receiving no medication.

Hypothesis 4b: Patients with polyprophylactic medication reach a higher DM-Risk-Score compared to patients with monotherapy.

Hypothesis 4c: Patients receiving Olanzapine reach a higher DM-Risk-Score compared to patients with no medication.

Hypothesis 4d: Patients receiving lithium reach a higher DM-Risk-Score compared to patients with no medication.

Literature suggests that there are differences in the pooled prevalence of diabetes mellitus regarding the different types of clinical classification (19).

Research question 5: Are there differences in the diabetes risk between BIP I and BIP II?

Hypothesis 5a: BIP I patients reach a higher DM-Risk-Score score compared to BIP II patients.

Hypothesis 5b: A higher depression-mania ratio is associated with a higher DM-Risk-Score.

Recent literature postulates that inflammation might be an influencing factor for the development of type-II Diabetes in bipolar disorder (29). Therefore, the question arises if patients in our cohort with higher levels of low-grade inflammation perform a higher score in the DM-Risk-Score.

Research question 6: Are there connections between low-grade inflammation and our defined DM-Risk-Score?

Hypothesis 6a: A higher C-reactive-protein (CRP) is associated with a higher DM-Risk-Score.

Hypothesis 6b: A higher Interleukin-6 (IL-6) is associated with a higher DM-Risk-Score.

3 Methods

The data for this thesis was collected as a part of the BIPFAT study protocol (EK Nr. 24-123 ex 11/12), which is continuously being conducted at the Research Unit for Bipolar Affective Disorders of the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University Graz.

3.1 Participants

For this thesis, a sample group of 245 patients with bipolar disorder and 142 mentally healthy controls was examined. The collective was between 18 and 82 years old.

Exclusion criteria for participants were current severe medical conditions, such as systematic lupus erythematosus, chronic obstructive pulmonary disease, neurocognitive and neurodegenerative disease, inflammatory bowel disease, active cancer and haemodialysis. Moreover, participants had to be of legal age in order to be included in the study. Before the inclusion into the study, all participants gave their written informed consent.

3.1.1 Patients

The cohort includes 245 patients (116 women and 129 men) who were recruited while being inpatients or as outpatients of the Research Unit for Bipolar Affective Disorders of the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University Graz. Patients' bipolar disorder diagnosis was verified using the SCID (Structural Clinical Interview), based on the DSM-IV diagnostic criteria. Moreover, the current mental state of the patients was evaluated using standardized external rating systems: HAMD (Hamilton Rating Scale for Depression) and YMRS (Young Mania Rating Scale). Current manic or severe depressive episodes lead to an exclusion of the study.

3.1.2 Controls

The cohort includes 142 healthy controls (88 women and 54 men). Controls were recruited from the general population. Exclusion criteria for the controls were past or current psychiatric episodes and diagnosis, severe medical conditions and first-degree relatives suffering from psychiatric diagnosis.

3.2 Procedure

Before including participants in the study, exclusion and inclusion criteria as mentioned above were evaluated. Fasting blood was taken, followed by a fixed breakfast. Next, a standardized anamnesis asserting demographic, psychiatric and medical information, anthropometric measures as well as neuropsychological tests were administered by trained investigators. Subsequent, numerous questionnaires, including the International Physical Activity Questionnaire (IPAQ) and Fragerström were completed by the participants. On a following date a brain MRT and a carotid sonography were conducted.

3.3 Material

The following chapter outlines the material used to collect the data for the examination.

3.3.1 Fragerström

The smoking habits were assessed with the Fragerström Test for nicotine dependence. The test contains six items that have to be answered by the test persons. In scoring, yes/no items are scored with 0 or 1 and multiple-choice items are scored from 0 to 3. The total score is obtained by adding the individual items. The internal consistency is $\alpha = 0,61$ and the re-test reliability is = 0,88 (39).

3.3.2 Body Mass Index

The BMI is calculated by dividing the weight in kilograms (kg) by the square of the height in meters (m). For this purpose the test persons were weighed on calibrated personal scales and measured (40). The Classification can be obtained in table 2.

Table 1: BMI-Classification

	BMI (kg/m2)
Underweight	< 18,5
Normal range	18,5 – 24,9
Overweight	25,0 – 29,9
Obese	> 30,0

Note: BMI= body mass index

3.3.3 Clinical Parameters

The clinical classification of BIP 1 or BIP 2 was verified by using the SCID. The number of phases was examined in a clinical-psychiatric interview.

3.3.4 IPAQ

In order to assess the physical activity behaviour of the participants, the long version of the self- administered IPAQ was used. The German version of the IPAQ-Long contains 27 items giving information concerning the duration and frequency in the last seven days of vigorous, moderate and low intensity activities in the four following domains: work, transportation, household and leisure activities. Additionally, sedentary behaviour is examined (41).

3.3.5 Medication questionnaire

As part of the clinical visit the current medication was interrogated and verified by checking patient's medical history. Relevant for this work was in particular mood stabilizing medication that in these analyses of data were all taken longer than one month.

3.3.6 Blood tests

Fasting blood was taken from all participants. For this work, special attention was paid to the blood sugar and lipid metabolism for which the clinical reference values were used.

Table 2: Overview over blood sugar and blood lipids

Blood values	**Cut-off range**	**Consequence**
Fasting plasma glucose	≥126 mg/dl	Diabetic
HbA1c	≥48mmol/mol Hb	Diabetic
Total cholesterol	>200mg/dl	Hyperlipidaemia
Triglycerides	>150mg/dl	Hyperlipidaemia
HDL	♂<35, HDL ♀<45 mg/dl	Hyperlipidaemia
LDL	>115mg/dl	Hyperlipidaemia
LDL/HDL-quotient	>3,4	Atherosclerotic-Risk↑

Note: HbA1c=Glycated haemoglobin A1c, Hb= Haemoglobin, LDL=Low Density Lipoprotein, HDL=High Density Lipoprotein

3.3.7 Risk score

The DM-RISK-Score was created on the base of found literature dealing with the screening of diabetes mellitus (42). Therefore, a score system consisting out of seven different items that all add up to a total score of seven points was defined. Following parameters were taken into consideration: (1) Patients that have a BMI bigger than 25, (2) a diabetes mellitus primary relative, (3) current hypertension or therapy, (4) low HDL or therapy, (5) high triglycerides or therapy, (6) a cardiovascular

event (e.g. heart attack or stroke) in the anamnesis or (7) raised blood sugar. Each of these parameters scored one point.

Table 3: Definition Diabetes-Mellitus-Risk-Score

Parameter	Interpretation	Score
BMI >25 kg/m2	overweight	1
DM primary relative		1
RR ⇑ > (140/90) mmHg	Hypertension or Therapy	1
HDL ⇓ < 35mg/dl	Reduced high density lipoprotein ("favourable cholesterol") or therapy	1
TG ⇑ >150mg/dl	Elevated triglycerides (blood fats) or therapy	1
CVD (status post)	Status post heart attack and/or stroke	1
BS ⇑ Glucose ≥6,9 mmol/or ≥126 mg/dl HbA1c ≥48 mmol/mol Hb	Elevated blood sugar in venous blood	1
Total Score		∑ 7

Note: BMI=Body Mass Index, RR=Riva Rocci, HDL=High Density Lipoprotein, CVD=Cardiovascular disease, BS=Blood Sugar, TG=Triglycerides, HbA1c=Glycated haemoglobin A1c, Hb= Haemoglobin

3.4 Analyses

The statistical analyses were done using the statistical program IBM SSPS version 22 for windows. T-test for unpaired samples, the chi-squared test and Pearson correlations and also univariate analyses (ANOVAs) were performed. The statistical significance was defined with a p value smaller than 0,05. All analyses were performed on separated groups, having one age group younger than forty-five (<45), the other greater or equal forty-five (≥45). Due to the fact, that data was collected in a prospective study with multiple parameters, n is sometimes smaller than 245.

4 Results

4.1 Descriptive statistics

In order to survey our cohort according to the predefined questions, we separated the sample into two age groups representing patients and controls either younger than forty-five (<45), or forty-five and older (≥45).

4.1.1 Description of patients and controls

The following table 4 shows the basic demographic information of the study cohort.

Table 4: Cohort description

	Patients	**Controls**
Male	52,7% (*n*=129/245)	38,0% (*n=54/142)*
Female	47,3% (*n*=116/245)	62,0% (*n=88/142)*
Age (years) *(M±SD)*	43,66±13,55 (*n*=245)	38,19±15,61 (*n*=141)
BMI (kg/m²) *(M±SD)*	28,21±6,03 (*n*=241)	24,66±4,83 *(n*=126)

Note: n=numbers, M=Mean, SD=Standard Deviation, BMI=Body Mass Index

4.1.2 Description of variables in the patient group

The following table 5 gives an overview over the variables used in the patient sample group younger than forty-five and in the patient sample group for the group forty-five and older.

Table 5: Variables description of patients

Patients (n=245)	**<45 years**	**≥45**
Smoking no	*n*=31	*n*=48
Smoking yes	*n*=46	*n*=19
	∑=77	∑=67
Low activity	*n*=33	*n*=28
Moderate activity	*n*=20	*n*=12
High activity	*n*=29	*n*=30
	∑=82	∑=70
BIP I	*n*=50	*n*=42
BIP II	*n*=28	*n*=24
	∑=78	∑=66
No medication	*n*=23	*n*=16
Lithium	*n*=16	*n*=17
Antipsychotics	*n*=21	*n*=17
Valproic acid	*n*=10	*n*=9
Combined medication	*n*=9	*n*=9
Lamotrigine	*n*=6	*n*=3
	∑=85	∑=71

Note: n=numbers, ∑= sum sign, BIP I, II= Bipolar classification

4.2 Metabolism in bipolar disorder and in the control group

In the following, it was examined whether there are differences between bipolar patients and healthy controls in the prevalence of diabetes mellitus, glucose and hba1c levels, as well as in our defined DM risk-score. The following table 6 shows the results for the sample group younger than forty-five.

Table 6.: Differences between bipolar disorder patients and controls in the glucose-metabolism in individuals <45 years

	Patients	**Controls**	***chi²/t***	***p***
DM	5,2% (*n*=7/134)	0%	4,693	**0,030***
Glucose *(M±SD)*	92,20±15,46 (*n*=131)	88,62±9,64 (*n*=85)	1,900	0,060
HbA1c *(M±SD)*	34,03±5,11 (*n*=126)	33,04±2,43 (*n*=84)	1,665	0,097
Risk-Score (M±SD)	1,8±1,28 (*n*=85)	0,79±1,11 (n=53)	121,653	**0,000***

Note: n=numbers, M=Mean, SD=Standard Deviation, DM=Diabetes Mellitus, HbA1c= Glycated haemoglobin A1c, **=p<0,05*

In the group younger than forty-five there has been a significant difference between patients and controls in the prevalence of suffering from diabetes mellitus and in achieving higher points in the DM-Risk-Score. No significance was shown in the levels of glucose and hba1c (see table 6).

Results for the group forty-five and older can be obtained in table 7.

Table 7: Differences between bipolar disorder patients and controls in the glucose-metabolism in individuals ≥45

	Patients	**Controls**	***chi²/t***	***p***
DM	9,5% (*n*=10/105)	2,3% (*n=1/43)*	2,30	0,13
Glucose *(M±SD)*	Pat.(*n*=97) 99,60±20,81	Pat.(*n*=41) 95,70±12,30	1,124	0,097
HbA1c *(M±SD)*	Pat.(*n*=95) 38,14±7,85	Pat.(*n*=41) 37,32±5,27	0,611	0,542
Risk-Score	Pat.(*n*=71) 2,46±1,38	Pat.(*n*=30) 2,27±1,46	99	0,519

Note: n=numbers, M=Mean, SD=Standard Deviation, DM= Diabetes Mellitus, HbA1c= Glycated haemoglobin A1c*, *=p<0,05*

In the group forty-five and older there has been no significant difference between patients and controls in the prevalence of suffering from diabetes mellitus. No significant difference was shown in the levels of glucose and hba1c nor in the performed DM-Risk-Score (see table 7).

4.3 Gender correlation of diabetes mellitus in bipolar disorder

In the following, it was examined if the diabetes mellitus differs in sex and which sex performs a higher score in the DM-Risk-Score. Only patients were examined in the following analyses. Results for the sample group younger than forty-five can be obtained in table 8.

Table 8: Gender related differences in prevalence of diabetes mellitus and DM-Risk-Score performance in individuals <45

	Male	**Female**	***chi²/t***	***p***
DM	4,2% (*n*=3/72)	6,5% (*n*=4/62)	0,351	0,553
Risk-Score *(M±SD)*	2,04±1,23 (*n*=48)	1,49±1,41 (*n*=37)	67,820	**0,047***

Note: n=numbers, M=Mean.SD=Standard Deviation, DM= Diabetes Mellitus, *Significance=p<0,05*

In the group younger than forty-five there has been no significant difference in the prevalence of suffering from diabetes mellitus regarding sex. Nevertheless, male patients performed a significant higher score in the DM-Risk-Score (see table 8).

Results for the group forty-five and older can be obtained in table 9.

Table 9: Gender related differences in prevalence of diabetes mellitus and DM-Risk-Score performance in individuals ≥45

	Male	**Female**	***chi²/t***	***p***
DM	15,1% (*n*=8/53)	3,8% (*n*=4/52)	3,854	0,050
Risk-Score *(M±SD)*	2,76±1,28 (*n*=37)	2,15±1,44 (*n*=34)	69	0,630

Note: n=numbers, M=Mean, SD=Standard Deviation, DM=Diabetes Mellitus, *Significance=p<0,05*

In the group forty-five and older there has been no significant difference in sex concerning the prevalence of suffering from diabetes mellitus and the performance in the DM-Risk-Score (see table 9).

4.4 Correlation between unhealthy lifestyle and diabetes mellitus

In the following, it was examined if there is a connection between unhealthy lifestyle factors and the risk to develop diabetes.

Figure 1 illustrates the difference between smoking/non-smoking in the DM-Risk-Score in both age groups.

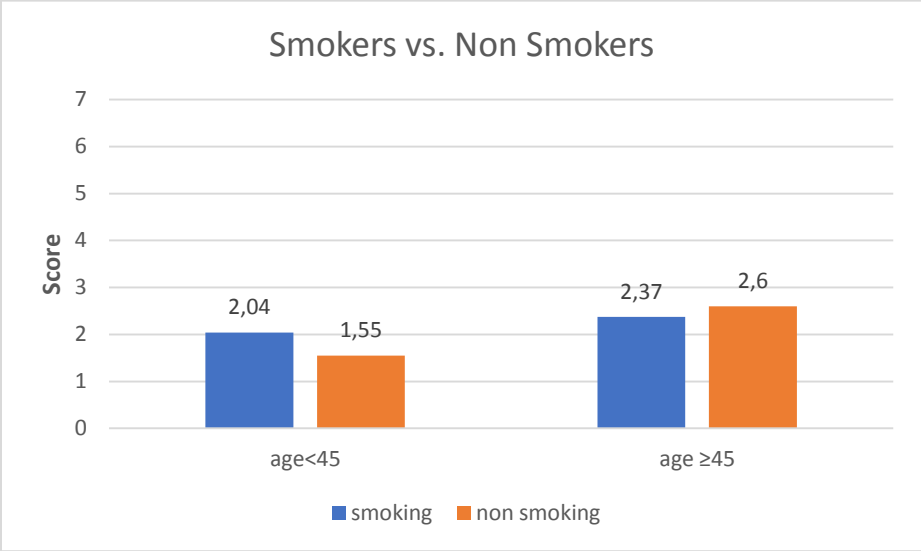

Figure 1: Difference between smokers and. non-smokers regarding DM-Risk-Score performance in both age groups

There was no significant difference found between smokers and non-smokers concerning the performance in DM-Risk-Score (t=75; p=0,104) in the group younger than forty-five. Also, there was no difference found in the group forty-five and older (t=65; p=0,528) (see figure 1).

Figure 2 below illustrates the difference between activity levels (high, moderate, low) and the performance in the DM-Risk-Score in both age groups.

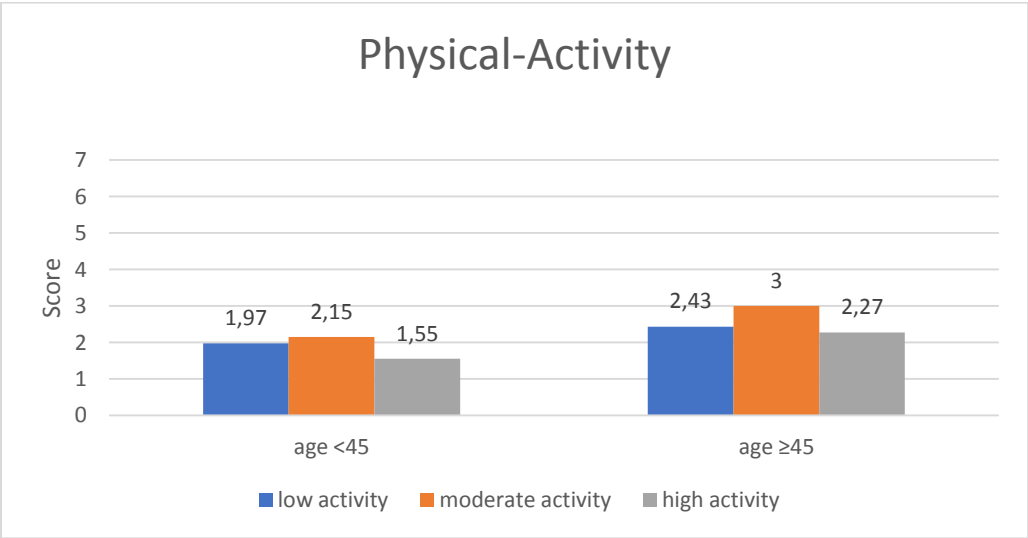

Figure 2: Relationship between physical activity and DM-Risk-Score performance in both age groups

There was no significant difference (*F* 2/82=1,556; *p*=0,217) found on between the different activity levels in the performance in the DM-Risk-Score in the group younger than forty-five. Also, there was no significant difference (*F* 2/70=1,210; *p*=0,305) in the group forty-five and older (see figure 2).

4.5 Correlation between medication and DM-Risk-Score performance

In the following it was investigated if there are differences in the DM-Risk-Score when administered different pharmaceuticals.

It was examined whether there is variation in the DM-Risk- Score if patients were administered lithium, antipsychotics, lamotrigine, valproic acid, combined medication (at least two different pharmaceuticals) or no medication. Results can be obtained in figure 3.

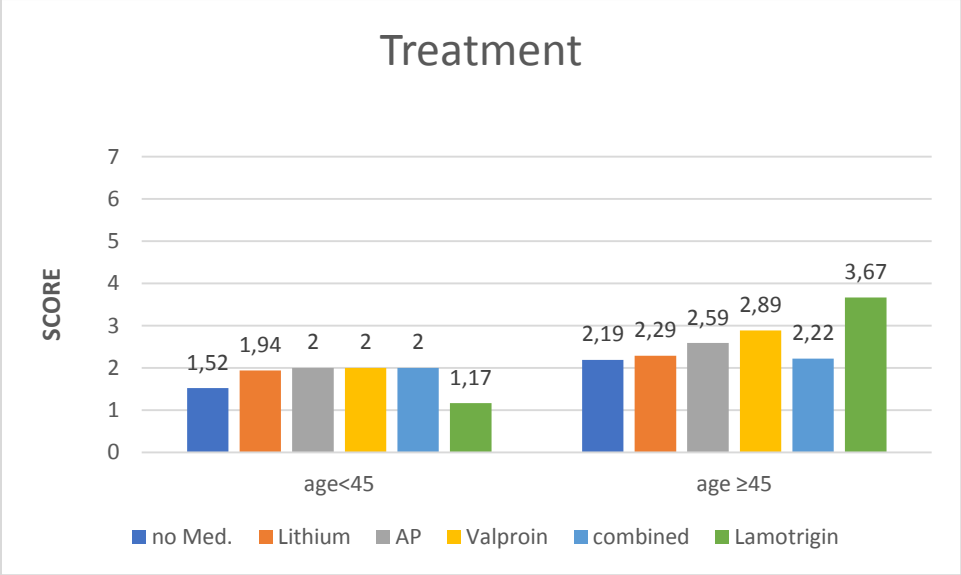

Figure 3: Difference between individual treatment in DM-Risk-Score performance in both age groups

There was no significant difference (*F* 5/85=0,732, *p*=0,602) found on Diabetes-Risk-Score performance after being administered different medication, combined medication and no medication in the group younger than forty-five (see figure 3). Also, there was no significant difference (*F* 5/71=0,879; *p*=0,500) in the group forty-five and older (see figure 3).

Further, it was examined if patients with polytherapy (more than 1 pharmaceutical) medication reach a higher score than patients with monotherapy. Results can be obtained in figure 4.

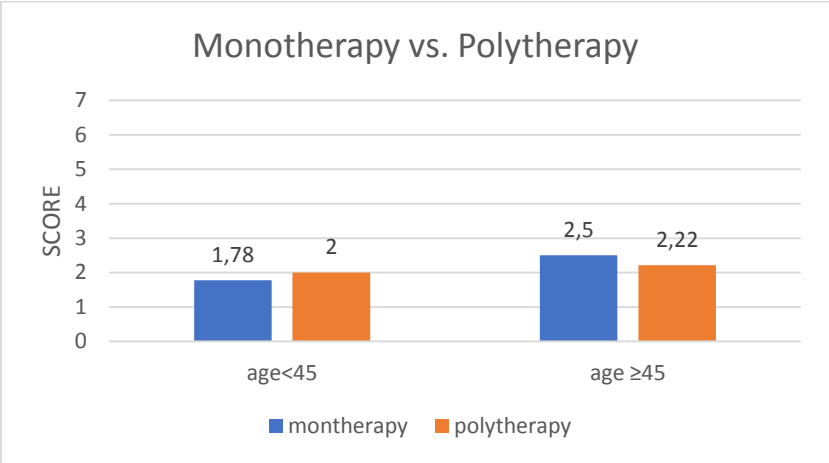

Figure 4: Correlation between monotherapy/polytherapy and DM-Risk-Score performance

There was no significant difference (t=83; p=0,623) found on Diabetes-Risk-Score performance after being administered poly-medication as opposed to monotherapy in the group younger than forty-five (see figure 4). Also, there was no significant difference (t=69; p=0,577) found on Diabetes-Risk-Score performance after being administered poly-medication as opposed to monotherapy in the group forty-five and older (see figure 4).

Further, it was examined if patients that were administered Olanzapine reach a higher score in the DM-Risk-Score compared to if no medication is given. This information can be obtained in figure 5.

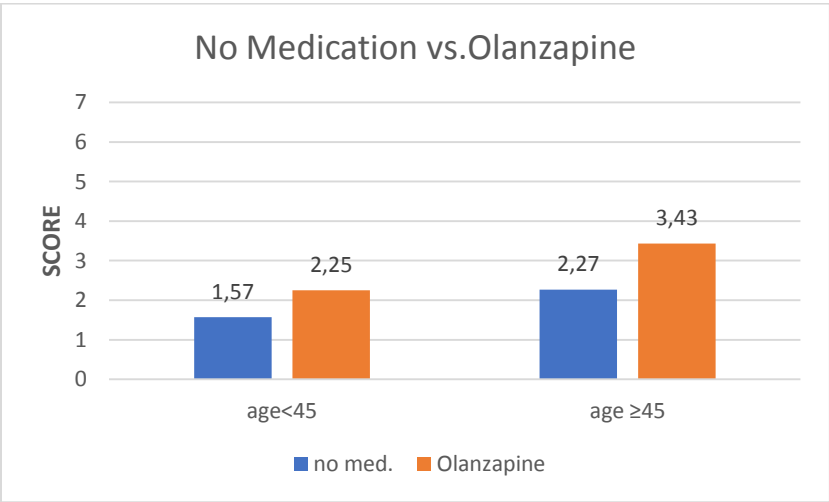

Figure 5: Differences in DM-Risk-Score performance between no medication versus Olanzapine

There was no significant difference (t=23; p=0,377) found on Diabetes-Risk-Score

performance after being administered Olanzapine as opposed to if no medication is given in the group younger than forty-five (see figure 5). Also, there was no significant difference (*t*=20; *p*=,054) found on Diabetes-Risk-Score in the group forty-five and older (see figure 5).

Further it was examined whether there is a difference in the performance in the DM-Risk-Score if patients are administered Lithium versus patients who receive no medication (see figure 6).

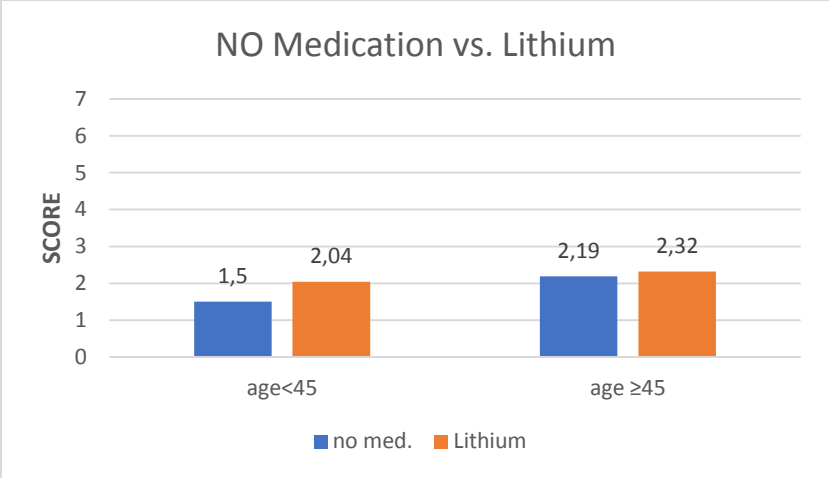

Figure 6: Differences in DM-Risk-Score performance between no medication versus Lithium

There was no significant difference (*t*=47; *p*=0,166) found on Diabetes-Risk-Score performance after being administered Lithium versus no Medication in the group younger than forty-five. (see figure 6) Also, there was no significant difference (*t*=36; *p*=0,750) in the group forty-five and older (see figure 6).

4.6 Differences between Bipolar I and Bipolar II in the DM-Risk-Score

In the following it was examined if there are differences between BIP I and BIP II patients concerning the performance in the DM-Risk-Score (see figure 7).

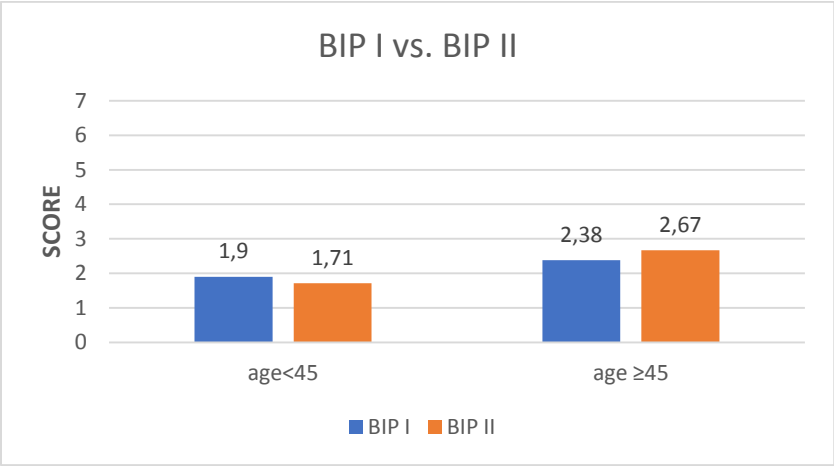

Figure 7: Differences in the DM-Risk-Score between BIPI and BIPII in both age groups

There was no significant difference (t=76; p=0,546) found on how the classification differences between BIP I versus BIP II effect the performance in the DM-Risk-Score in the group younger than forty-five (see figure 7). Also, there was no significant difference (t=64; p=0,424) in the group forty-five and older (see figure 7).

Further it was examined if the depression-mania ratio correlates with the performance in the DM-Risk-Score. In the group younger than forty-five no significant correlation (r=0,062; p=0,602) could be found. Also, there was no significant correlation (r=-,015; p=0,904) in the group forty-five and older.

4.7 Correlation between low grade inflammation and the DM-Risk-Score

In the following the connection between low grade inflammation and the DM-Risk-Score were examined. There was no significant difference found between the level of low grade inflammation parameters CRP (r=0,072; p=0,515) and IL-6 (r=-,112; p=0,312) and the performance in the DM-Risk-Score in the group younger than forty-five. However, there was a significant difference found between the level of low grade inflammation parameters CRP (r=0,386; p=0,001) as well as IL-6 (r=0,377; p=0,001)

and the performance in the DM-Risk-Score in the group forty-five and older. The higher the low-grade inflammation, the higher the DM-Risk-Score. The information can be obtained in figure 8 and 9.

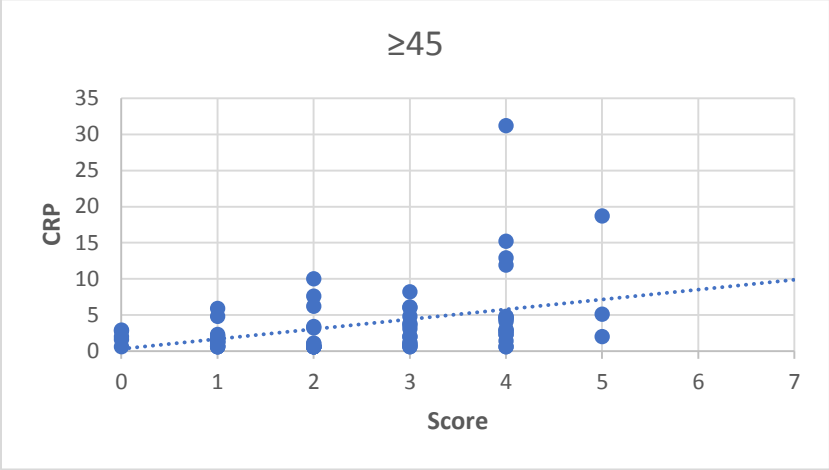

Figure 8: Correlation between CRP and the DM-Risk-Score in the group forty-five and older.

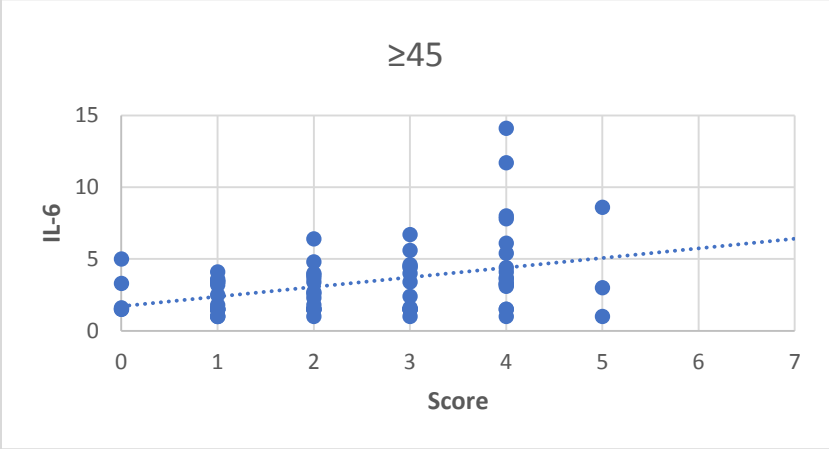

Figure 9: Correlation between IL-6 and the DM-Risk-Score in the group forty-five and older.

5 Discussion

This study investigated the connection between type-II diabetes mellitus in patients suffering from bipolar disorder and compared it to a group of healthy controls. As expected, the prevalence of suffering from type-II diabetes mellitus was higher in bipolar patients than in healthy controls. Regarding the glucose metabolism, the DM-Risk-Score performance showed a significant difference in the age group younger than forty-five. Sex differences could be illustrated in the group younger than forty-five, here it was shown that male patients performed a significant higher DM-Risk-

Score. Also, a correlation between low grade inflammation and bipolar disorder could be reproduced, here it was shown that higher inflammation was associated with higher performance in the DM-Risk-Score in the group forty-five and older. While literature revealed some interesting aspects about the connection of diabetes mellitus and bipolar disorder, most of these findings could not be replicated in this study.

5.1 Discussion of the results

The next chapter is concerned with discussing the results of the statistical analysis and to compare them with the results of the literature research.

5.1.1 Metabolism in bipolar disorder and in the control group

When comparing the differences in the glucose metabolism of patients with bipolar disorder to controls representative for healthy population, a significant higher prevalence of diabetes mellitus II as well as a higher DM-Risk-score was found in individuals with bipolar disorder in the age group younger than forty-five. Especially the higher prevalence of type-II diabetes mellitus met our expectation since previous literature already postulates that the risk of suffering from type-II diabetes in individuals with psychiatric disorders is three times as high compared to mentally healthy people (3). Nevertheless, results from other studies found the prevalence of type-II diabetes mellitus approximately numbered with 10%. Also it seems that the variance of diabetes mellitus type-II prevalence in the general population contributes largely to the variance in diabetes prevalence in people with bipolar disorder implying that a higher prevalence of diabetes mellitus in the general population, leads to a higher prevalence of diabetes mellitus within people who suffer from bipolar disorder (18). We were not able to analyse this in our sample as in our control group no one suffered from diabetes mellitus II. It might further be assumed, that individuals with bipolar disorder treated at the research unit for bipolar disorder are more regularly controlled not only for their mental but also for their somatic health compared to patients not treated at a specialized institution. Therefore, prevalence rates of DM might vary from our sample. It has been furthermore claimed in literature than there is a high proportion of undiagnosed diabetes mellitus (42).

Despite the higher prevalence of diabetes mellitus and higher DM-risk-scores in younger patients we could not find significantly higher fasting blood glucose level or

elevated hba1c in individuals with bipolar disorder compared to control subjects. Considering that literature described association between higher hba1c levels and symptoms of depression in patients with bipolar disorder (43), our pre-defined hypotheses and expectations were not met in the current sample.

On the contrary to our expectations in the group forty-five and older no hypothesis could be confirmed. These were built on the fact that the American Diabetes Association recommends screening for type-II diabetes annually in patients forty-five years and older, clearly indicating that the risk of suffering from diabetes mellitus rises with age (41). As the sample size in the group forty-five and older was relatively small, in order to show a significant association, it might have been necessary to enlarge the sample group for forty-five and older to find statistically significant effects.

5.1.2 Differences between men and women concerning diabetes mellitus in bipolar disorder

According to found literature, there seem to be differences regarding gender in the prevalence of diabetes mellitus when suffering from bipolar disorder. Women are at greater risk of suffering from diabetes mellitus across all ethnic and racial groups. In particular glucose and lipids were dysregulated at high rates in patients with bipolar disorder ,especially when female and over forty (21). Hypothesis 2a stating that women with bipolar disorder suffer more often from diabetes mellitus than men with bipolar disorder could not be verified. In our investigation, no significant difference in the prevalence of type-II diabetes regarding gender could be reproduced in both age groups. On the contrary, it must be pointed out that in the group forty-five and older 15,1% of male patients suffered from diabetes mellitus and the criteria for having a significant difference were nearly met, *p* being 0,050. Also, hypothesis 2b suggesting that women in comparison to men have a higher DM-Risk-Score could not be verified. In the group younger than forty-five the opposite was the case showing that men performed significantly higher points in the DM-Risk-Score. In the group forty-five and older there was no significant difference in the performance in the DM-Risk-Score.

In Summary the role of gender still remains controversial , not only is there very little information concerning gender prevalence, also there have been studies claiming

that gender is not a moderating variable (19), hence further research on the role of gender needs to be performed.

5.1.3 Correlation between unhealthy lifestyle and diabetes mellitus

According to the hitherto literature the prevalence of smoking is significantly higher in bipolar disorder compared to the general population (44). Furthermore, patients with bipolar disorder have higher rates of other somatic comorbidities, which is associated with higher mortality rates and worse course of illness (45). Common predictors of somatic comorbidity are unhealthy lifestyle factors like smoking and sedentary lifestyle (18). In contrast to our expectations, smokers with bipolar disorder did not have a higher DM-Risk-Score compared to patients who did not smoke in our sample. There was no significant difference between smokers and non-smokers in the DM-Risk-Score independent of age. Even more, no significant difference between bipolar individuals with low, moderate and high activity levels in the DM-Risk-Score could be found.

At this point it has to be mentioned that the IPAQ is a subjective questionnaire of physical activity. In comparison to known behaviour in the general population, patients and controls reported to spent too little time with sedentary behaviour and exaggerated with time spent with physical activity limiting the objective meaningfulness of the survey.

Overall, literature indicates clearly that diabetes mellitus type-II can be prevented through diet and lifestyle modification (46) because a sedentary behaviour is clearly associated with a 112% increase in the relative risk of suffering from diabetes mellitus (36). Overall it is known that physical exercise increases the glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin resistant subjects (47). Yet, only few studies exclusively examined lifestyle modification in people with bipolar disorder. One study, however, compared two groups after applying to one group randomly a special designed bipolar care program consisting of symptom control strategies, education and behavioural change related to cardiovascular disease risk factors. It showed that, after receiving this care program in opposite to the group that did not receive care, the decline of physical health-related quality of life may have been slowed down (48). Another study showed that the participants, after receiving a cognitive-behavioural therapy-based lifestyle

modification program weight, cholesterol and triglycerides decreased as well as their daily sugar and calories consummation, when more exercise was performed and depressive symptoms and functioning improved (49).
Since it seems that the hypothesis that the prevalence of type-II diabetes mellitus in people with bipolar disorder is likely to be related to the general population an adoption of a healthy lifestyle and behavioural changes should not only occur in people with bipolar disorder but also be emphasized in the general population.

5.1.4 Correlation between medication and DM-Risk-Score performance

There is a lot of literature linking diabetes mellitus as an unintended medication side effect in the treatment of bipolar disorder (37), especially antipsychotics but also mood stabilizers or antidepressants are held responsible. There is literature indicating that treatment of patients with bipolar disorder with mood stabilizers like lithium and valproic acid can exacerbate risk factors for diabetes mellitus type-II such as weight gain and craving for fast food fats. Therefore, we looked into differences between groups of pharmaceuticals in the DM-Risk-Score. No significant differences between the medication classes could be found, even more, between mono- or combination- therapy could be found. Nevertheless, as expected, in the group younger than forty-five antipsychotics, lithium and combined medication reached descriptively ex aequo the highest points in the DM-Risk-Score, in the group forty-five and older lamotrigine performed the best in the DM-Risk-Score.
Further, hypothesis 4c postulating that patients receiving olanzapine reach a higher DM-Risk-Score than patients with no medication could not be verified. On the contrary to our expectation, since antipsychotics, especially atypicals like clozapine and olanzapine are linked with a diabetogenic side effect since they inhibit insulin secretion by antagonizing acetylcholine muscarinic 3 receptors in the β-cells of the pancreas (50) (51), no significant difference was found on DM-Risk-Score performance between olanzapine compared to no medication was found. For both age groups, it has to be noted that the number of patients receiving Olanzapine was very small, which limits validity of results. In order to show an association as postulated in literature, a bigger sample is needed.
The diabetogenic side effect of psychotropic pharmaceuticals in the treatment of patients with bipolar disorder remains unclear. In our calculations, it could not be

reproduced which could be owed to the small sample group. However it could also support the hypothesis which suggests that there is a medication independent association which is also described in literature (52) since the higher incidence of diabetes mellitus in patients with bipolar disorder still remains unexplained especially in treatment naïve patients (53) (54).

5.1.5 Differences between Bipolar I and Bipolar II in the DM-Risk-Score

Literature suggests that there is an association between abnormal glucose metabolism and bipolar disorders (55). In patients with bipolar I disorder the pooled prevalence of diabetes mellitus type-II was found to be 12,1% and 8,7% in patients with mixed diagnoses (bipolar I and bipolar II) (18). Based on this information we looked into the differences of clinical classification and the performance in the DM-Risk-Score. However, hypothesis 5a stating that BIP I patients reach a higher DM-Risk-Score score than BIP II patients could not be verified.
Elevated hba1c levels as mentioned above are associated with depression but also depression itself is considered as a risk factor for suffering from diabetes mellitus (56) (57). However, hypothesis 5b postulating that the higher the depression-mania ratio the higher the DM-Risk-Score could not be verified, no significant correlation could be found in the group younger than forty-five and in the group forty-five and older.

5.1.6 Correlation between low grade inflammation and the DM-Risk-Score

A lot of research has been undertaken on immune dysfunction paired with chronic inflammation conferring risk for both diabetes mellitus and bipolar disorder (58). Supported by the fact that patients with bipolar and also patients with diabetes mellitus disorder are found to have increased susceptibility to allergies and elevated pre-inflammatory markers (59) we searched for a connection between low grade inflammation and our defined DM-Risk-Score. In our sample, an association between CRP and the DM-Risk-Score could be found as expected in the group forty-five and older. On the contrary to our expectation, no significant association was found between the level of low grade inflammation parameter CRP and the performance in

the DM-Risk-Score in the group younger than forty-five. It can be assumed that the immune system of younger people is still functioning better than it does in elderly people and therefore no correlation could be found.
Hypothesis 6b postulating that the higher the IL-6 the higher the DM-Risk-Score was also confirmed in the group forty-five and older. There was a significant correlation between the level of IL-6 and the performance in the DM-Risk-Score in the group forty-five and older. On the contrary to our expectation, there was no correlation found in the group younger than forty-five. Also, here it can be assumed that the immune system of younger people is still functioning better than it does in elderly people therefore there is less inflammation.
It can be summarized that in the group forty-five and older higher inflammation leads to a higher DM-Risk-Score supporting found literature that inflammation might be a crucial factor for the development of diabetes mellitus type-II in patients with bipolar disorder. The identification of inflammatory markers present in the medical condition of bipolar disorder and diabetes mellitus will enable researchers and clinicians to better understand the aetiology of bipolar disorder and develop treatments that simultaneously target all aspects of this multi-system condition (60).

5.2 Discussion of methods

While the neurocognitive test battery, the laboratory markers and the standardized anamnesis have shown to be very valid in previous investigation; the DM-Risk-Score was applied for the first time in the study group.

5.2.1.1Risk score

According to the American Diabetes Association early screening and more frequent monitoring should take place if considered a high-risk patient. Since literature indicates that patients with a bipolar disorder are at a threefold higher risk of suffering from diabetes mellitus we created a “risk-score” which oriented itself on the baseline of diabetes risk and the ensuing screening suggestions by the American Diabetes Association. Inspired by these recommendations we narrowed down our DM-Risk-Score to seven items consisting of anthropometric values such as the BMI, the medical history including family history of diabetes (primary relative) and personal

history of cardiovascular events, individual blood sample where HDL, TG, glucose and hba1c were taken into account and last but not least the blood pressure. Because the age itself is considered a risk for diabetes mellitus we separated the patients and controls into two groups having one group younger than forty-five and one group forty-five and older. By applying this score, we were able to reproduce found facts in the beforehand conducted literature research. However, for the blood lipids only HDL and TG were considered, not taken into consideration was the total cholesterol amount, the LDL and the LDL/HDL-quotient. For the HDL value, we chose to take the reference cut-off of <35mg/dl which is suitable for male patients rather than <45mg/dl which is suitable for women. Also, not included in the DM-Risk Score and also not treated as an individual hypothesis, yet for further appliance definitely recommended would be dietary habits. Smoking habit could be included in the DM-Risk Score as an individual item and also lifestyle habits if quantifiable could be taken into consideration. Further thyroid abnormalities which have been convincingly associated to bipolar disorder (62), where investigations focus on finding a link between thyroid abnormalities, diabetes mellitus and mood symptoms (63) and sleeping abnormalities which are often found in people with bipolar disorder and which are seen as a contributing factor to the development of diabetes mellitus could supplement the DM-Risk Score.

5.3 Limitations and Improvements

The DM-Risk Score has to be mentioned as the main limitation of the study. We selected the DM-Risk Score based on a previously conducted comprehensive literature research. The items chosen and abstracted however provide a subjective point of view since not all parameters which were suggested could be taken into consideration. Other important lifestyle factors such as nutrition are missing. The size of the sample group was 387 in total out of which there were 245 patients and 142 healthy controls allowing a representative statement.

In our investigations, we could not apply the DM-Risk Score to each subject of the sample group.

While the parameters for gender, age, BMI and glucose metabolism could be applied to the entire sample group, certain parameters such as clinical classification, and medication could not be applied to the healthy control group because these subjects

do not have a clinical diagnose and do not receive medication. Lifestyle, inflammation and gender prevalence of diabetes mellitus variables were also only examined in the patient group. Due to the fact that we did not have the complete numbers for all variables of the entire patient group, the figures at which we arrived do not give a representative picture because *n* was lower than the number of the patient sample group.
Should further research based on these parameters be carried out, we would recommend taking a larger sample group to get a more conclusive result.

5.4 Conclusion

In conclusion, it should be said that screening proactively for diabetes mellitus is a clinical imperative in patients suffering from bipolar disorder for which the DM-Risk Score could be of used, since in this high-risk population diabetes mellitus is associated with a reduced quality of life (64), a higher mortality risk than the general population (65) and increased medical cost (66).

6 Bibliography

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