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Prevalence of Metabolic Syndrome Among Psychiatric Inpatients. Literature Review

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1. AIMS AND OBJECTIVES

The main purpose of this literature analysis is to review and discuss different common psychiatric diseases, their pathology, treatment options, patient groups with regard to the prevalence of metabolic dysregulations. This paper mainly focuses on diseases such as major depression, bipolar, disorders, psychotic disorders and anxiety disorders, since these conditions are mostly associated with the prevalence and development of the metabolic syndrome. In addition to that, some physiological and neuroendocrine foundations of the above-mentioned mental diseases are covered and explained in more detail. Also, a perspective into treatment options, lifestyle factors and prevention such as the M.O.B.I.L.I.S program is drawn.

2. KEYWORDS

Metabolic syndrome, ATP III, IDF, dyslipidemia, triglyceridemia, insulin resistance, diabetes mellitus, hypertension, obesity, HDL, LDL, cholesterol, abdominal obesity, DSM-V, major depression, bipolar disorder, psychotic disorders, anxiety disorders, SSRI, TCA, mirtazapine, dopamine, serotonin, 5-HTC, noradrenaline, HPA-axis, CRH, ACTH, cortisol, leptin, leptin resistance, inflammatory cytokines, chronic inflammation, olanzapine, clozapine, lithium, valproate, smoking, nicotine, alcohol, M.O.B.I.L.I.S

3. METHODS

In this paper, a systematic literature review was conducted on the various etiological, pathophysiological, and therapeutic aspects of the prevalence of the metabolic syndrome among psychiatric inpatients. The literature search strategies included Google scholar, PubMed scientific database, Elsevier, Springer, scientific papers, academic books, and was limited to articles available in English and German language. The majority of papers were published in the years 2000 to 2020. For this study, the author reviewed 49 publications in total. Literature selection criteria included subjects diagnosed with serious mental illnesses according to the DSM-5 criteria. All participants displayed components of the metabolic syndrome. Concomitant diseases were excluded. Participants were predominantly both male and female middle-aged Caucasians, as well as Asian and African-Americans subjects. Due to limited data available, other psychiatric diseases were not discussed in this paper. Children and adolescents were excluded since the majority of metabolic and cardiovascular manifestations mainly affect the older population.

4. INTRODUCTION

The Metabolic syndrome by definition is a complex disease pattern associated with high socioeconomic costs and considered as a rising worldwide epidemic. This condition is characterized by a combination of various interconnected factors that drastically increase the risk to develop coronary heart disease (CHD) and Diabetes mellitus type 2(DMT). The most widely known laboratory components, such as dyslipidemia (elevated triglycerides) and apolipoprotein B-containing lipoproteins, as well as reduced High-density lipoproteins (HDL) are considered as atherogenic factors. The presence of Hypertension and a dysregulated glucose homeostasis (elevated plasma glucose) are major components. Insulin resistance and abdominal obesity are the main drivers of the Metabolic syndrome, while other concomitant conditions such as physical inactivity, aging, hormonal imbalances and a diet rich in cholesterol and saturated fats, further increase the risk of cardiovascular events(1).

Recent suggestions have linked the Metabolic Syndrome to proinflammatory and prothrombotic states, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome and sleep apnea. However, this cluster of metabolic dysregulations and the exact pathologic mechanism is still not entirely understood, and there are no universally accepted criteria. Five different systems of clinical diagnosis of the metabolic syndrome are known, and they have been modified in the recent years. These Systems include the WHO (1998), EGIR, ATP III (2001) AACE (2003) and IDF (2005) criteria.

The most recent definition of the Metabolic Syndrome was published by the US National Cholesterol Education Programme Treatment Panel III (NCEP ATP III) guidelines in 2005. The Diagnosis could be established if three or more of the following listed conditions are present: Hypertension (≥130/85 mmHG), fasting plasma glucose was or ≥= 6.1mmol/L, fasting plasma triglycerides ≥ or =1.69 mmol/L , fasting HD-cholesterol <1,04 mmol (males) or 1.29 mmol (females), and a waist circumference greater than 88cm (males) or 102cm (females)(1).

The ATP III criteria are commonly used in medical practice and epidemiological studies and their utility is characterized by favouring multicausal rather than monocausal variables. Another clinically widely distributed classification system used for the Metabolic Syndrome is by the International Diabetes Federation (IDF), which shares similar definitions related to

syndrome. The main difference is that the ATP III considers abdominal obesity as one out of several possible diagnostic factors, while in contrast, the IDF sets this as a fixed requirement. The following table summarizes the recent diagnostic ATP III criteria.

TABLE 2. Criteria for Clinical Diagnosis of Metabolic Syndrome

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

(1)

5. DEPRESSION

Major depressive disorder is as a medical condition characterized by abnormalities of affect and mood, cognitive symptoms such as inappropriate guilt, feelings of worthlessness, and vegetative symptoms such as loss of appetite or sleep disorders. Psychomotor activity,

including symptoms like agitation or retardation, may also be affected. Major Depression is one of the oldest, best-known medical disorders, with multifactorial etiological factors involving biological, socioeconomic, and psychological factors. The monoamine hypothesis, established in the 1950s, links major depression to reduced levels of monoaminergic neurotransmitters such as serotonin, noradrenaline, and dopamine(2). Different subtypes of depression are recognized, with atypical depression characterized by an increase in appetite and body weight and major depressive disorder with psychotic features characterized by hallucinations and delusions. According to the DSM-V, a major depressive disorder is diagnosed if at least 5 symptoms persist every day over the course of 2 weeks (3). Symptoms commonly reported include abnormalities of affect and mood, neurovegetative symptoms like loss of appetite or sleep disturbances, and psychomotor symptoms like agitation or retardation. Treatment options for major depressive disorder include both behavioural cognitive therapy and pharmacotherapy. Various drug classes, such as selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and monoamine oxidase inhibitors (MAOIs) have been proven effective in clinical practice. However monoamine oxidase inhibitors are not routinely used due to their severe adverse drug reactions, such as overdose, serotonin-syndrome and hypertensive crisis, which can occur if tyramine-containing foods, such as cheese or red wine, are consumed(4).

5.1. CORRELATION BETWEEN METABOLIC SYNDROME AND DEPRESSION

According to 29 cross-sectional studies by Pan et al, 155 333 patients diagnosed with clinical depression or self-reported symptoms a modest association with an adjusted odds ratio OR=1.34 between metabolic syndrome and depression was found(5). Another correlation was found in the Netherlands Study of Depression and Anxiety among 3000 subjects were examined. The most important outcomes are the existence between depression and markers of obesity such as central obesity, decreased HDL-Cholesterol, hypertriglyceridemia. Coexistence of Hypertension or hyperglycemia on the other hand was reported seldomly.

The presence of a bidirectional relationship between MS and depression was confirmed by a systematic review and meta-analysis study, which observed seventeen studies including 31880 people. (OR= 1.51, CI 95%= 1.36-168) and cohort studies (OR=1.6, CI 95% =1.23 -2.08).

There is a suspicion that metabolic syndrome and depression can influence each other in both ways. Metabolic syndrome can cause depression and vice versa, which can be mostly explained by the activation of the hypothalamus-pituitary-adrenal axis. The human body's stress system consists of two components: the HPA axis and the sympathetic nervous system. Acute stressors trigger the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus and corticotropin-releasing factor, and arginine vasopressin (AVP). These pathways cause the release of ACTH (adrenocorticotropin hormone) from the neurohypophysis and noradrenaline from the locus caeruleas, which both cause the fight and flight response. ACTH promotes cortisol secretion from the zona fasciculata of the adrenal gland, which normally follows circadian cycles with the highest cortisol concentration in the early morning hours. Suffering from chronic stress, including psychological stressors seen in depressed patients, can induce HPA-axis dysregulations that cause imbalances in target organs, such as an increase in visceral adipose tissue.

The presence of Depression is also correlated with patient non-adherence to treatment and poor lifestyle choices, including a poor diet, smoking and alcohol consumption, lack of sleep, and lower activity levels, which, in turn can cause metabolic dysregulations such as obesity(6). Thakore et al. stated that patients with major depression showed a significantly higher visceral body fat than healthy controls. Furthermore, a significant correlation between plasma cortisol and visceral body fat, as well as cortisol and waist-to-hip ratio, was found(7). According to a study from 2002, Weber-Hamann et al. could prove a significant increase in the volume of visceral body fat only among patients with depression and accompanying hypercortisolism, in comparison to depressed patients with normal cortisol levels. A Follow- up study showed that, compared with healthy controls with a similar rate of weight gain, depressed patients had a significantly higher amount of visceral body fat(8).This effect was not correlated with whether the patients were normo- or hypercortisolemic.

Visceral adipose tissue is associated with an increased risk of cardiovascular events and diabetes compared to subcutaneous fat due to increased metabolic activity. The SWAN-study, which included 409 middle-aged women, demonstrated a strong correlation between the presence of depressive symptoms and the accumulation of visceral body fat(9). In 2005, Kahl et al. examined patients diagnosed with MDD and those with comorbid borderline-personality disorder. They measured visceral body fat, insulin sensitivity, serum interleukin-6 (IL-6), fasting cortisol, tumor necrosis factor-alpha (TNF), beta cell sensitivity using the homeostasis

assessment model, and compared them to 20 healthy women and 12 BPD patients. According to their findings, both patient groups showed increased levels of visceral body fat, putting them at risk of developing noninsulin-dependent diabetes mellitus (NIDDM) features of the metabolic syndrome. Increases in cytokine levels, and endocrine dysregulations favours both depression and metabolic complications, such as ischemic cardiovascular events(10).

5.2. ANTIDEPRESSANTS

SSRIs are a drug class primarily used to treat depression. Due to their clinical safety, efficacy and tolerability, they are used not only as a first-line pharmacological treatment, but also in a variety of other psychiatric disorders and can be used in adult and paediatric patients. Drugs like Fluoxetine or Escitalopram are often used to treat conditions like MDD, generalized anxiety disorder, obsessive-compulsive disorders or post-traumatic stress disorders. Off-label use includes conditions like binge-eating disorders, premature ejaculation, or fibromyalgia. Because of their lower side effect profile, they are used more frequently compared to agents from drug classes like MAOIs or TCAs. According to their labelling, SSRIs work by inhibiting the reuptake of serotonin, increasing serotonergic activity and involve neurotransmitters such as dopamine, noradrenalin, acetylcholine only to a minor degree. The side effect profile includes sexual dysfunction, sleep disturbances, weight changes, gastrointestinal distress and QT-interval prolongation(11). The question of whether SSRIs can cause metabolic disturbances is not yet completely understood. A few studies have confirmed the connection between SSRI use and gain in visceral body fat and increased serum cholesterol levels(12).

Data from The Hordaland Health Study contained a general community cross-sectional health survey, including 25,315 participants between 40 to 49 and 70 to 74 years old. For each group the prevalence and odds ratio (ORs) for obesity, an increase in serum cholesterol, HDL, hypertriglyceridemia, and diabetes were observed. Associations between SSRIs intake (N=461) and abdominal obesity, hypercholesterolemia was found. Especially the subgroup, taking paroxetine (N=187) showed a significant increase in abdominal and general adipose tissue, but no association with hypercholesterolemia was found. Citalopram users (N=142) did not show any associations with MS parameters, whereas patients using sertraline or fluoxetine (N=131) showed a correlation with increase in both above-mentioned metabolic parameters(13). It was recommended, that SSRI users should undergo careful monitoring of dyslipidemia and obesity.

Tricyclic antidepressants (TCAs), including agents like amitriptyline, doxepine, or nortriptyline are mainly indicated for major depressive disorders. TCAs and SSRIs are equally effective in treating mood disorders, but differ in their side effect profile. TCAs, in general, have more pronounced anticholinergic activity and a reduced threshold for toxicity, so they are not routinely used as first-line drugs(14). Off label conditions such as migraine prophylaxis, OCD, anxiety or chronic pain are certain targets of its use. TCAs mainly work by blocking the reuptake of serotonin and norepinephrine in presynaptic clefts, which leads to an increase in these neurotransmitters. Another effect is the competitive antagonism on cholinergic, histaminergic and muscarinic receptors. Several adverse drug reactions have been reported due to the competing sub-receptors, including constipation, dizziness, blurred vision, urinary retention, and tachycardia, among others(15). Due to their H1-antagonism effects, like sedation, hyperphagia, weight gain and confusion have been confirmed(16).

According to a cross-sectional study that examined 294 patients with bipolar disorder, using SSRIs, TCAs, and SNRIs while diagnosing MS according to the NCEP ATP-III criteria, the following outcomes were found: In general, no significant correlation was found between the use of antidepressants and MS ([PR], 1.08; 95% confidence interval, 0.73 to 1.62; p = 0.70). However, among subjects using antidepressants affecting the histaminergic blockade (N=15), a signifcant increase in the prevalence of MS parameters was found (PR, 2.17; 95% confidence intervall, 1.24 to 3.80; p = 0.007)(17). Licht et al. obtained cross-sectional data in a large cohort study (N=590) and showed that the use of TCAs is asscoiated with higher mean systolic and diastolic blood pressure and a greater likelihood of being diagnosed with Hypertension stage 1 and 2 (odds ratio: 1.90; 95% CI:0.94 to 3.84; P = 0.07), (odds ratio: 3.19; 95% CI: 1.35 to 7.59; P = 0.008) (18).

5.3. MIRTAZAPINE

Mirtazapine is classified as an atypical antidepressant, technically belonging to the tetracyclic antidepressant drug class and is mainly used to treat major depressive disorders. Its pharmacological effect is similar to other antidepressants, working by inhibiting presynaptic alpha-2-adrenergic, 5-HTA, 5-HTC and 5-HT3 serotonergic receptors, leading to an increased level of serotonin and noradrenalin. Due to its potent antagonisitc effect on H1-histamine receptors, which is responsible for causing a sedating and calming effect in patients, it is often

used as an off-label agent to treat conditions like insomnia, panic disorders, post-traumaticstress disorders (PTSD) or social anxiety disorders. Its adverse effects include drowsiness, weight gain, increased serum cholesterol, increased appetite, sedation and hypertriglyceridemia(19). More seldom side effects include bone marrow suppresion, neutropenia and acute pancreatitis. Due to numerous drug interactions, mirtazapine should be avoided when using substances with other sedative properties like diazepam, tramadol, ketoconzalole because the sedative effects can drastically increase(19).

With regard to the metabolic effects of mirtazapine, it is worth mentioning the following two studies. Linda M Nicholas et al. Performed a double-blind design with 50 healthy participants including 30 women and 20 men. The subjects recieved either mirtazapine 15 mg (N=28) or placebo (N=22) over a period of 4 weeks. Parameters like lipoproteins, triglyerides, LDL, HDL were measured on a weekly basis while increasing the dose up to 30 mg daily. The mirtazapine group gained 2.5% in mean body weight, while no changes were found in the control group. After 4 weeks, the same group showed a significantly increase in plasma triglyerides ($p = 0.16$), which normalized after 4 weeks, while the other parameters were mostly unaffected(20). Hennings et al. could show that mirtazpine use (30mg) over a 3 week period is associated with increased hunger and appetite for sweet foods and an increase in insulin and C-peptide(21). Although, no changes in terms of weight gain or resting energy expenditure were observed.

6. BIPOLAR DISORDER

Bipolar affective disorder is a major cause of worldwide disability, with a lifetime prevalence that accounts for 1% of the general population. Most studies suggest an equal distribution of this disorder between men and women, although, some authors in the literature suggest a higher prevalence of bipolar type 1 in males and more cases of bipolar type 2 disorder in women. Manic-depressive disorder is a complex and chronic mental illness and consists of a combination of manic, hypomanic and depressive states(22). Patients suffering from this disorder experience functional disability and impaired quality of life. Bipolar Type I is characterized by at least one lifetime manic episode sufficient to diagnose this disorder, although depressive symptoms in between have also been reported. The diagnostic criteria of type II BD are at least one hypomanic episode without any manic episodes in the past, with the absence of substance, iatrogenic agents, or organic causes. Cyclothymic disorders are another disease morphology, that shares more similarities with personality disorders.

The disease can start in the early adulthood (18-20 years), but can also have a later onset of first clinical symptoms. Etiological factors include either biological (genetic, anatomical, hormonal), or psychosocial (stressors) causes. Causative factors consist of either biological (genetic, anatomical, hormonal), or psychosocial triggers. It is thought that dysregulations in biogenic amines, such a dopamine, serotonin, norepinephrine and second messengers like cyclic adenosine monophosphate (cAMP), can cause Bipolar disorders(22). The clinical diagnosis of Bipolar disorder is complex and is based on the DSM-5 criteria(22).

Therapeutic options include pharmacotherapy using mood stabilizers (such as lithium), antipsychotics, and anticonvulsants such as carbamazepine or valproic acid. Lithium is considered the gold standard in long-term management and can decrease the risk of suicide(22). Atypical antipsychotics can be combined with mood stabilizers or used as a monotherapy. Treatment-resistant acute episodes can be treated with electroconvulsive therapy, which is also suitable for pregnant woman(22).

According to McElroy et al, 644 patients were assessed, among 58% had obesity, 21% were overweight, and 5% were extremely obese. Compared to European patients, significantly higher BMI rates were found among American patients. A considerable correlation was found between male sex and the presence of hypertension and adiposity(23). Yumru et al. observed a significant association of the metabolic syndrome with users of atypical antipsychotics(24). According to a statement of the European Psychiatric Association, weight gain of 4.45kg and 4.15kg after a 10-week period was described among clozapine and olanzapine users (25). A literature analysis published in 2009 showed a connection between therapeutic amount of atypical antipsychotics intake and rate of weight gain(26). It is assumed that weight gain, primarily is caused by medication-induced increase in appetite and excessive caloric intake. The exact underlying mechanisms are still under observation(25).

Guha et al. conducted a study among subjects newly diagnosed with bipolar disorder, that were pharmacologically naive for at least 6 months. No significant deviations with regard to the HDL-values and hip-to-waist ratio were found. However, increased values were observed for serum triglycerides, blood pressure, insulin resistance and fasting plasma glucose. The presence of metabolic syndrome was equal in both groups and was not correlated with age, sex, or current psychiatric condition(27). Increased LDL and triglycerides, low HDL in combination

with lack of physical activity are strongly correlated to development of the metabolic syndrome and cardiovascular diseases(28). Pharmacological agents used to treat bipolar disorders, such as lithium, valproic acid and olanzapine are associated with an increase abdominal fat mass, especially central obesity(29).

Several different pharmacological agents, such as statins, fibrates, Cholestyramine or PCSK9-inihibitors are used to lower increased serum cholesterol levels, which are associated with a risk of cardiovascular events. Researchers from the United Kingdom investigated 587 general practitioners to estimate the effects of statin use for primary prevention of cardiovascular disease and lipid modification in schizophrenic and bipolar patients. Both groups were categorized as statin users and non-users. The study showed that the incidence of cardiovascular diseases could not be significantly reduced in statin-users. However, the subjects using statins, showed a 27% reduction in total cholesterol (1.7 mmol/L). The serum cholesterol of statin-naive subjects could only be reduced 2% (0.1mmol/L)(30).

7. SCHIZOPHRENIA

Schizophrenia is a chronic psychiatric disorder characterized by symptoms like delusions hallucinations, disorganized speech, behaviour and impaired cognitive abilities. Both, the early onset and the chronicity of this condition, makes it a challenging disorder for patients and families of affected individuals. Negative symptoms, such as loss of interest, impaired verbal or emotional expression are accompanied by positive symptoms, like suspiciousness, delusions and hallucinations(31). Pathophysiological abnormalities include either an excess or deficiency in neurotransmitters like dopamine, serotonin and glutamate. Additionally, it is hypothesized that aspartate, glycine and even gamma-aminobutyric acid (GABA) play a role in its pathogenesis.

Excess levels of Dopamine in the mesolimbic pathways are thought to be responsible for the positive symptoms of schizophrenia. Motor symptoms can be explained by a relative dopamine deficiency in the nigrostriatal pathway which expresses the extrapyramidal system. The brain in schizophrenic patients shows an increase in volume of the third and lateral ventricles, as well as reduced areas in the medial temporal lobe(31).

Dopaminergic deficiencies in the mesocortical pathways can explain the spectrum of negative symptoms. Endocrine deficiencies such as amenorrhea or reduced libido, arise with increased prolactin levels, resulting from a blockade of the tuberoinfundibular dopamine(31). Causative mechanisms include genetic susceptibility and environmental factors such as childhood trauma, social isolation or discrimination. Schizophrenia has a prevalence of 0.6 % to 1.9 % in the U.S. Males and females are equally affected, but males are more likely to experience their first episodes in their early 20s while females in general are affected in their early 30s.

When patients experience their first psychotic episode, social withdrawal or schizoid behaviours are prominent signs(31). As mentioned above, positive symptoms include delusions, hallucinations, abnormal motor behaviour. Negative symptoms such as avolition, or diminished emotional expressions along with alogia and anhedonia are typical, but difficult to diagnose since, also medication, or environmental factors can cause such effects.

7.1. ANTIPSYCHOTICS

Two different types of antipsychotics are indicated for the treatment of schizophrenia. Typical antipsychotics (first-generation) are dopamine receptor antagonists and include substances from the phenothiazine group such as trifluoperazine or perphenazine, as well as butyrophenes such as haloperidol, which is the most commonly used. Other types are thioxanthenes (thiothixne, chlorprothioxene) or dibenzoxazepines (loxapine). Their mechanism of action is the inhibition of the D2 dopamine receptors in the brain. In addition, noradrenergic, cholinergic and histaminergic blockade are typical effects. The side effect profile includes a risk of significant extrapyramidal, and/or anticholinergic effects such as dry mouth, constipation, urinary retention. H-histaminergic blockade is responsible for sedating effects. Chlorpromazine hast the highest sedative potential compared to fluphenazine or haloperidol. Other reported effects include arrhythmia and antiepileptogenic effects. Contraindications include a history of allergy and the use of concomitant CNS depressants such as barbiturates or opioids.

On the other hand, second-generation antipsychotics are termed as atypical antipsychotics and display their pharmacological effect slightly differently, by blocking serotonin-dopaminergic pathways. According to the Food and Drug Administration, 12 atypical antipsychotics, such as risperidone, olanzapine or quetiapine have been approved. In comparison to first generation

antipsychotics, SGAs have decreased extrapyramidal side effects but are associated with significant weight gain and the development of the metabolic syndrome(32).
Remarkable side effects include QTc prolongation, orthostatic hypotension and dizziness. Contraindications include pregnancy, an increased incidence of stroke and dementia in elderly patients due to cholinergic side effects. Second-generation atypical antipsychotics such as risperidone or ziprasidone show efficacy in first-line treatment of schizophrenia(33).They work as antagonists of dopamine D2 receptors but are also shown to have serotonergic properties (5-HT1A, 5- HT2A)(34).Because there is a risk of agranulocytosis, clozapine is not generally recommended.

Second-generation antipsychotics are associated with fewer extrapyramidal symptoms, but their metabolic profile in terms of weight gain, hyperlipidemia and diabetes is worse(34). Increased incidences of the metabolic syndrome have been found in schizophrenic patients. In a cross-sectional study that included 15 schizophrenic subjects, Thakore et al. were able to show that schizophrenic individuals displayed an increased amount of visceral fat distribution. Visceral adipose tissue accumulation, considered as a pathological risk factor, was not dependent on pharmacotherapy(35).Abdominal computed tomography scanning showed, that schizophrenic patients had 3.4 times more intra-abdominal fat mass compared to normal control group ($p < .005$)(29).

Littrell et al examined the prevalence of insulin resistance among 98 outpatients and 27 inpatients diagnosed with schizo-affective disorders, using the homeostasis model assessment (HOMA-IR) consisting of fasting insulin and glucose levels.70% of outpatients and 44% of inpatients revealed a significant degree of insulin resistance(29). Outpatients were American individuals and inpatients were individuals from Taiwan.

R. Rosmond et al. observed the correlation between the HPA-axis dysregulation and various components of the metabolic syndrome in schizophrenic subjects(36).The HPA-axis is a complex closed endocrine feedback system that stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland via the release of corticotropin releasing hormone (CRH) from the hypothalamus resulting in normal physiological plasma cortisol levels. However, cortisol levels during early sleep could not be sufficiently inhibited by the dexamethasone suppression test. Higher cortisol levels during the daytime could be related to positive symptoms of schizophrenia such as delusion or hallucinations(36).The hunger

hormone leptin plays a remarkable role in satiety, and disturbances in the HPA axis, that lead to insufficient leptin signals and could be associated with weight gain and obesity(37).

Weight gain is a common sight effect using antipsychotic medication, and the rate of weight gain depends on the dose and type of drug. Specifically clozapine and olanzapine are associated with the highest risk of weight gain compared to haloperidol, lurasidone or ziprasidone(38). Agents like Clozapine cause leptin resistance in the central nervous system, which further causes an increase in appetite, weight gain, and increased leptin secretion to compensate the defective signalling(37). Muhkerjee et al. observed that the diagnosis of schizophrenia itself, is a risk factor for developing glucose intolerance and/or type II diabetes mellitus. Patients who did not use neuroleptic medication were more likely to have diabetes than the group that was on medication(37). The author performed another study to confirm the suspicion. In conclusion, no diabetogenic effects related to the administration of the drug haloperidol were proved, while repeatedly measuring oral glucose tolerance. This result is also strengthened by the fact that on average18%-30% of patients with schizophrenia have a positive family history of type 2 diabetes and also high rates of insulin resistance, and impaired glucose tolerance before treatment induction(37).

Several studies have proved evidence that certain atypical antipsychotics, especially clozapine are associated with hypertriglyceridemia. In a prospective study, subjects were treated with clozapine for 12 weeks and developed an increase in serum triglycerides, while all other lipid parameters did not increase. The study examined two patient groups over the course of 6 months. The first group was neuroleptic-resistant and treated with clozapine, while the other subjects were treated with typical antipsychotics. As a result the clozapine group showed increases in serum triglycerides, while the other group showed elevated serum cholesterol levels(39). It is worth mentioning that olanzapine can cause both elevated cholesterol and hypertriglyceridemia(37).

8. ANXIETY/PANIC DISORDERS

Anxiety disorders are one of the most common psychiatric disorders and are thought to be caused by an interplay of biopsychosocial factors. Genetic factors, paired with stressful or traumatic situations tend to be responsible for the clinical symptoms. Variables like

medications, substance abuse, trauma or childhood experiences can trigger anxiety events(40).The prevalence varies depending on the type of disorder. Specific phobias display a 12-month prevalence rate of 12.1%, followed by social anxiety disorder (7.4%). Agoraphobia has a prevalence of 2.5% and is the rarest type.

Neurotransmitters involved in anxiety are noradrenalin, serotonin, dopamine and GABA, which also directly affect the sympathetic nervous system, which is responsible for most of the symptoms(40). The amygdala, together with the limbic system, serves as a control centre in the brain, mediating responses to anxiety triggers. Clinically relevant symptoms of anxiety include fear of losing control, fear of injury or death, fear of going crazy. Moreover, symptoms like poor concentration, confusion, distractibility, or poor memory are reported. Psychological symptoms are often times accompanied by physical discomfort, such as tachycardia, palpitations, chest pain or shortness of breath.

The management of acute anxiety includes the short-term use of benzodiazepines, while chronic anxiety treatment focuses on psychotherapy, or long-term pharmacotherapy. Pharmacological agents include benzodiazepines, such as alprazolam or lorazepam, SSRIs (fluoxetine, sertraline), SNRIs (venlafaxine, duloxetine) or tricyclic antidepressants (amitriptyline, nortriptyline). Beta-blockers are shown to be effective in reducing sympathomimetic symptoms. Cognitive-behaviour therapy is the most effective form of psychotherapy especially in the long term(40).

Data on the prevalence of metabolic syndrome among patients with anxiety disorders is not clear. Skilton et al. found a higher prevalence of metabolic dysregulations in Patients with a comorbid depression, but not specifically with anxiety(41).

Kahl et al conducted a study of 260 subjects, among which150 were at risk for T2DM. The study found that 27% of males and 25% of females and the metabolic syndrome. The study also presented significant associations between having a current anxiety disorder ($P < 0.001$) and major depression ($P < 0.001$), and the occurrence of metabolic syndrome(42). Single anxiety symptoms are connected to some psychiatric diseases for instance in major depression, or subtypes of depression but only few data specifically related to anxiety are available.

Participants from the Netherlands Study of Depression and Anxiety (N=2.776) were interviewed with regard about their depression and anxiety symptoms. All 5 laboratory parameters of the metabolic syndrome were measured. A correlation was found between depressive and anxiety symptoms, particularly in triglycerides and waist circumference. Anxiety is a common symptom in various psychiatric disorders and can interfere and individual's daily life choices and perception of the world around them. Whether anxiety disorders themselves, or anxiolytic medication contribute to metabolic and cardiovascular risk factors is required further research.

9. NEUROENDOCRINE, METABOLIC AND IMMUNE DYSREGULATIONS

Physical, and psychological stressors can disturb the homeostasis of the human body. Because stress is a central part of the human life, the body has adapted certain systems to restore normal homeostasis. As mentioned earlier, the HPA axis, together with the sympathetic nervous system, is a substantial part of acute stress regulation. Furthermore, stress can also affect the gastrointestinal barrier by increasing the gut microbiome permeability, which can affect the integrity of the blood-brain-barrier (BBB). It is assumed that the intestinal gut microbiota is in direct contact with our central nervous systems and can induce changes in the HPA-axis response(6,43). Whether or not this is the key to our mental well-being is not entirely understood. Elevated ACTH and morning cortisol levels were reported in bipolar disorders and in psychotic patients. Higher cortisol levels could be linked to manic episodes, whereas negative associations were found in patients using antipsychotics(6).

Technically, the result of body fat accumulation is the consumption of excess calories via hypercaloric, mostly ultra-processed foods and a lack of physical exercise, resulting in an overall net caloric surplus. Two different types of body fat are distinguished brown adipose tissue (BAT) and white adipose tissue (WAT). Brown adipose tissue (BAT) is metabolically active and contains a high number of mitochondria, and its main function is the generation of heat. White adipose tissue (WAT) serves as a long-term fat storage and excess of WAT predisposes to different cardiovascular events such as Type II DM. Furthermore, WAT is considered as a unique endocrine organ that secrets a variety of up to 600 hormones and mediators such as adipokines, cytokines, leptin, and vasoconstrictors (angiotensin II), which play an important role in almost all pathological processes in our body. Dietary lipids,

especially polyunsaturated fatty acids, tend to activate cellular immune responses by secreting cytokines like IL-1, IL-6, TNF-alpha, CRP, to name a few.

A complex interplay between these modulators and our immune system initiates a systemic pro-inflammatory state in the body(44). Further accumulation of adipose tissue creates a vicious circle of diminished hunger signals due to defective leptin signalling, leading to insulin resistance. Pro-inflammatory cytokines tend to interfere with either the synthesis, or secretion of the monoamines, dopamine D2, serotonin and noradrenaline, which are involved in many psychopathological processes either in excess or deficiency(44).

Inflammatory cytokines have the ability to cross the blood-brain barrier and serve as modulators that interfere with normal serotonin synthesis. This process affecting the kynurenine pathway, which is a metabolite of tryptophan and creates toxic metabolites such as glutamate residues or free radicals that impair neuronal transmission and lead to damaged neurons(45). According to Shelton et al., there is a bidirectional relationship between depression and Obesity. Chronic inflammation due to increased circulating fatty acids can cause depression, and vice versa, depression can cause obesity(44).

Hypercortisolemia is closely linked to depression. This could be explained by the ability of inflammatory cytokines to modify and inhibit glucocorticoid receptors in the HPA-axis, leading to glucocorticoid resistance. This hypothesis was proven by infusing IFN-alpha in patients undergoing cancer treatment. The following response was a rise in ACTH release from the pituitary and cortisol from the adrenal glands(44).

10. LIFESTYLE FACTORS

Individuals with mental illnesses tend to make worse lifestyle choices, such as smoking, alcohol and substance abuse, lack of physical activity, which increases their health risks. Healthy dietary habits are necessary to reduce the risk of cardiovascular events. Variables such as psychiatric symptoms and socioeconomic status significantly influence health-related decisions. Affected individuals often show symptoms such as apathy, social isolation and loss of motivation, which make it difficult for them to practice adequate self-care. Feelings of hopelessness, which is often seen in depression, negatively influence their health behaviour. Moreover, the social environment plays a significant role in health behaviour. Mentally ill people often live in isolation and have small and weak social networks(46).

Regarding nutrition, the literature consistently shows that patients with psychiatric disorders tend to consume foods that are high in fat, salt, and sugar, and low in fibre, leading to dissatisfaction with their meals (46). Brown et al. (1999) found that schizophrenic patients consumed diets poor in fibre and high in fat content, and none of the subjects in the study met the recommended intake of five servings of fruits and vegetables per day. Additionally, schizophrenic patients tend to eat less in the morning, and consume more processed foods in the evening(47).

Furthermore, schizophrenic patients have a higher likelihood of avoiding physical activity, which is often exacerbated by unemployment. Patients with affective disorders often report experiencing early fatigue and anhedonia after engaging in minimal physical activity(46).

Leas et al. could find another correlation between schizoid, and affective disorders and smoking(46). The theory of self-medication assumes, that nicotine increases the dopamine effect and has the potential to reduce the negative symptoms of schizophrenia(46).

Meanwhile, Roick et al. investigated the drinking behavior of schizophrenic patients and obtained mixed results, with some patients showing increased tendencies to consume alcohol while others exhibited a reduced desire to drink(47).

11. PREVENTION AND TREATMENT

The main target of managing the metabolic syndrome consist of reducing the risk for clinical atherosclerotic disease, by lowering LDL-cholesterol, blood pressure and treating diabetes. Priority is given on improving underlying risk factors such as obesity, physical inactivity and diet. If a high risk for future cardiovascular events still persist, pharmacological interventions should be considered. Weight reduction can be achieved by lowering caloric intake by 500 to 1000 kcal per day for a period of up to 1 year, combined with more than 30 minutes of moderate-intensity exercise on most days of the week. Statins and triglyceride-lowering drugs such as fibrates and nicotinic acid, can be used if the LDL target is not reached.

The management of hypertension consists of angiotensin-converting-enzyme (ACE) inhibitors as a first-line therapy, which can be replaced by angiotensin II-receptor-blockers (ARBS) in patients who do not tolerate ACE inhibitors.

Patients with impaired fasting plasma glucose (IFG) can achieve glucose targets by adding metformin or thiazolidinediones(1).

Second generation antipsychotics, by far have to most potential for weight gain compared to other psychotropic pharmaceuticals. As mentioned earlier, histaminergic affinity, especially on the H1 receptor(48) and 5-HT2c polymorphism play a central role in energy homeostasis and subjective increase in appetite and food intake. Maayan et al. performed a double-blind, placebo-controlled trial on drugs that target antipsychotic-induced weight gain. Fifteen different substances, including amantadine, dextroamphetamine, fluoxetine and metformin, were tested, while measuring BMI, waist circumference, parameters of glucose and lipid metabolism, and psychiatric symptoms. Metformin showed to have the biggest effect on weight loss, followed by d-fenfluramine, sibutramine and reboxetine(48). Metformin was only effective after weight gain has occurred, but not when used concomitantly with antipsychotics. Furthermore, a meta-analysis of 10 behavioural intervention studies (n=482) showed that nutritional interventions had similar effects on treatment outcomes as cognitive behavioural therapy(48).

Because of the long-term detrimental effects of metabolic syndrome on cardiovascular health, the Freiburg University Hospital and the German Sports Academy (Deutsche Sporthochschule) in Cologne developed a program called M.O.B.I.L.I.S. The background of this project is to develop an interdisciplinary training program, targeting the treatment of obesity and accompanying risk factors (49). This project aims to motivate patients to change their behavior and lifestyle choices for better health outcomes in the future. The program has four central topics: (exercise/sport, psychology/instruction, nutrition, and medicine). The team consists of sport scientists, psychologists, nutritionists and doctors and aims to lower risk factors and improve the quality of life. Patients with conditions like type 1 diabetes, liver and kidney damage, or cancer patients in remission were excluded.

During a period of 12 months, 4000 to 5000 obese subjects were required to follow a standardized training program with predetermined time intervals. Specific body weight, body mass index (BMI) and waist circumference goals were established for the participants. The total cost for the program was 785, but according to Article 43 No.2 of the SBG V, the costs were refundable.(49).

The results of this project were remarkable, with 32 groups have completing the 12-month project and 454 out of 517 registered participants successfully completing it, while 12.2% of the participants failed to complete it. The participants were 75.4% women and 24.6% men. The success of the subjects was independent of age and BMI, and was equally distributed between men and women(49). The exact results showed a weight reduction of 6.4 kg in one year for all subclasses, having a (400kcal/day) deficit per day. This program provides an effective example of how the combination of proper diet and regular exercise has a beneficial effect on all parameters of the metabolic syndrome.

12. CONCLUSION

The metabolic syndrome is a rising disease pattern in modern society, caused by a variety of interconnected factors that ultimately lead to an increased risk of cardiovascular events such as myocardial infarction or stroke. The most important causative components are unhealthy lifestyle choices such as lack of physical activity, a diet consisting of mostly ultra-processed, calorie-dense foods that are rich in saturated fats, refined sugar and salt. This drives insulin resistance, hypertension and finally obesity. Especially psychiatric inpatients have a greater risk of developing metabolic dysregulations compared to the normal population. The most common affected parameters among this patient group are dyslipidemia, abdominal obesity, hypertension and hyperglycemia. However, finding data supporting Hypertension as a risk factor in general was reported rather seldomly. The scope of this literature review was to compare different psychiatric diseases, their pathology and pharmacotherapy regarding to metabolic dysregulations.

Patient suffering from Depression tend to have increased levels of cortisol and visceral body fat. Hypercortisolemia due to internal or external stressors is associated with weight gain, especially visceral body fat. Controverse results were shown in studies observing the use of antidepressant drugs. In general, the use of SSRIs and TCAs is not necessarily associated with metabolic dysregulations. Only slight systolic and diastolic blood pressure elevations were reported in subjects using TCAs. On the other hand, the use of mirtazapine, which is classified as an atypical antidepressant, is associated with increased risk of weight gain due to increase in appetite and craving for sweet foods.

Additionally, the use of paroxetine, sertraline and fluoxetine, displayed significant negative effects on the metabolic profile. Nevertheless, correlations were found in bipolar patient groups. Increased rates of hypertension, obesity, and weight gain are found in the literature, mainly associated with the use of antipsychotics like olanzapine and clozapine. Also drugs like lithium, valproic acid potentially led to an increase in abdominal fat mass.

Neuroleptics like olanzapine and clozapine, by far are the most well-known and well-studied drugs to cause weight gain and increase in blood lipid parameter. According to the literature several explanations were hypothesized. Deficient leptin signaling, H2-antihistminergic actions leading to an increase in appetite and consequently to an accumulation of a calorie surplus. The role of the metabolic syndrome among patients suffering from anxiety or panic disorders is less clear. Some correlations were found between the metabolic syndrome and single anxiety symptoms but not anxiety disorders themselves.

In general, psychiatric patients are predisposed to worse lifestyle choices, which could be explained by social isolation, stigma, financial difficulties and a lower socioeconomic status. These variables are observed in most psychiatric illnesses, and most of these patients showed metabolic dysregulations previous starting pharmacotherapy. Psychiatric patients often feel unsatisfied and compensate, by indulging in hedonistic behavior like smoking, drinking, gambling or unhealthy food choices that cause instant gratification but is detrimental long-term.

Patients should be educated on nutrition and exercise programs that could be affordable and easy to maintain long-term. Moreover, it is necessary to control the metabolic risks and side effects of psychotropic medication by monitoring the blood lipid panel in a regularly. Preventive programs such as M.O.B.I.L.I.S potentially could reduce the burden of the metabolic syndrome in the future.

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